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HEREDITY COUNSELING

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Managing Editor, Eugenics Quarterly



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Participating Authors

JOHN C. BUGHER, M.D.
Director for Medical Education and Public Health, The Rockefeller Foundation, New York

SHIRLEY S. BUTTERS, R.N.
Public Health Nurse Field Worker, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda

LEE R. DICE, PH.D.
Professor Emeritus of Zoology, University of Michigan, Ann Arbor

HAZEL R. DYSON, R.N.
Public Health Nurse, Section on Human Genetics, National Institute of Dental Research, National Institutes of Health, Bethesda

HAROLD F. FALLS, M.D.
Associate Professor of Ophthalmology and Research Associate, Department of Human Genetics, University of Michigan, Ann Arbor

F. CLARKE FRASER, M.D., PH.D.
Associate Professor of Genetics, McGill University; Director of Medical Genetics, Montreal Children's Hospital, Montreal

BENTLEY GLASS, PH.D., S.D., LL.D.
Professor of Biology, Johns Hopkins University, Baltimore

C. NASH HERNDON, M.D.
Chairman of Department of Preventive Medicine and Genetics, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem

FRANZ J. KALLMANN, M.D.
Chief of Psychiatric Research (Medical Genetics), New York State Psychiatric Institute, Professor of Psychiatry, Columbia University, New York

VICTOR A. MCKUSICK, M.D.
Associate Professor of Medicine, Johns Hopkins University School of Medicine, Physician, Johns Hopkins Hospital, Baltimore

JAMES V. NEEL, M.D., PH.D.
Professor and Chairman, Department of Human Genetics, Professor of Internal Medicine, University of Michigan Medical School, Ann Arbor

CLARENCE P. OLIVER, PH.D.
Professor and Chairman, Department of Zoology, University of Texas, Austin

SHELDON C. REED, PH.D.
Professor of Zoology and Director, Dight Institute of Human Genetics, University of Minnesota, Minneapolis

WILLIAM J. SCHULL, PH.D.
Associate Professor of Human Genetics, Department of Human Genetics, University of Michigan, Ann Arbor

JOSEF WARKANY, M.D.
Professor of Research Pediatrics, University of Cincinnati; Children's Hospital Research Foundation, Cincinnati

CARL J. WITKOP, JR., D.D.S.
Chief, Human Genetics Section, National Institute of Dental Research, National Institutes of Health, Bethesda

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Foreword

One hundred years have passed since Gregor Mendel began his experiments with garden peas. Eight years of meticulous experimentation were summarized in a paper published in 1866 but which remained almost unknown for the next 34 years. Rediscovery of his principles by de Vries and others brought to light the forgotten former work and established terms such as "Mendel's law" and "Mendelian inheritance" in the language of genetics.

The early years of the present century saw the emergence of the concept of spontaneous and abrupt changes in inheritable characters and the relationship of such modifications to the course of evolution. That factors in the environment, such as radiation and chemicals, could produce inheritable changes in the germ cells was recognized although not fully appreciated. Work with *Drosophila* by Morgan, Muller, and others established a clearer understanding of the mechanisms of inheritance on a quantitative experimental basis. Not just the cell as a whole, but the minute structure of the chromosomes became the focus of attention Statistical concepts, correlated with intracellular morphology, became generalized as genetic principles applicable to higher mammals as well as to insects and plants.

Following a period when cellular morphology was the basis of genetic rationalization, there slowly developed the present period of emphasis on the molecular structure of the genetic material of the chromosomes. We gradually approach a more profound understanding of the nature of the gene and the manner in which comparatively minor permutations of the building blocks of desoxyribonucleic

of time required to establish the foundations of clinically useful human genetics.

It is only within comparatively recent times that our knowledge of human inheritance has developed to the point at which heredity counseling has become a valuable aspect of clinical medicine. The geneticist may now utilize the accumulated observations of many scientists who have worked over the past 50 years.

As knowledge has advanced, the techniques of genetic study have also improved. Through study of population isolates, it has been possible to extend the knowledge of the genetic structure of particular diseases within a comparatively brief span of time. The determination of the frequencies of particular manifestations has made possible the statement of the probability of occurrence of various disturbances in human development. The advice the geneticist may be able to give may often be of the greatest value in allaying anxiety on the part of parents or in guiding family planning.

Within recent years the young science of genetics has approached maturity and has been able to contribute not only to the solution of difficult medical problems but also to the formulation of national policy. The symposium presented in this volume is an attempt to relate recent developments to the background of genetic knowledge and to establish a good perspective of important medical and social problems having a genetic origin.

John C. Bucher

Director for Medical Education
and Public Health
The Rockefeller Foundation

acid in the germ cells may give rise to drastic modifications of the individual organism.

As one reflects upon the development of the science of genetics, one is struck by the comparative slowness with which understanding has grown. About one great step in a human generation has been the pace, each new advance having been slowly assimilated into the body of working knowledge. Following each step, generalizations based on oversimplification in the biologic sphere have developed. Apparently satisfactory hypotheses have later been characterized by myriad exceptions which have served to demonstrate the inadequacy of the theory. Thus knowledge has grown, until today there is what appears to be a reasonably satisfactory general body of knowledge concerned with the broad principles governing the inheritance of individual characteristics.

The application of genetic principles to human problems requires a substantial body of detailed information concerning the degree to which inheritance is involved in specific maladies. The understanding of the mechanisms requires the most careful accumulation of observations. Despite the relevance of general principles to various forms of life, extrapolation of genetic manifestations from one species to another is usually fraught with great uncertainty. The application of genetic knowledge in human situations requires the prior establishment of a sufficiently large number of observations based on individual family histories. The labor of the human geneticist is necessarily prolonged and slowly productive. Because the turnover rate of human populations is slow in terms of the time scale of the human observer, the task inevitably requires the accumulation of information through several lifetimes. No single observer can hope to encompass the entire span

of time required to establish the foundations of clinically useful human genetics.

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Preface

This book is a timely one. Through the words of the various distinguished experts who have contributed to it, it brings us up to date on some of the major problems of heredity in medicine and on the developing role of counseling those who seek genetic advice in marriage and reproduction. It is also timely because it focuses attention on an area that has been long neglected and sorely needs development if a sound understanding of the balanced interplay between environment and genetics is to be achieved and utilized in the conduct of our affairs.

Although the discoveries of the science of animal genetics are well known, extensively used, and widely celebrated as they, of course, deserve to be, it remains after more than half a century a deplorable situation that human genetics and the part it plays in our development is still relatively unexplored and often ignored. The time has long passed when students could seriously dismiss the significance of heredity in human variation. The inexorable fact is that we can never hope to understand man fully without a knowledge of his genetics.

The American Eugenics Society which sponsored the occasion for the following papers is happy to bring them to the wider public that their publication in this form permits It is indebted to the various authors and, in particular, to Drs John C Bugher and Bentley Glass for their skill in conducting their respective sessions.

HARRY L. SHAPIRO, *President*
American Eugenics Society

Introduction

JOHN C. BUGHER

There is no region of human experience that has quite the same content of emotional overtone as the relation of parent to child. Most people are far more concerned about the welfare of their children than they are about their own health and happiness. Consequently, the functions discussed in the following papers fall among those that come closest to the lives of people and their sense of values in the life of the individual as well as in the life of the family.

In genetic counseling one finds there are serious problems involved. We can say that the responsibility of the counselor falls into two distinctly different areas. One is the scientific content of his special field, the knowledge of genetics, and particularly the knowledge of human genetics. Despite the contrary opinions frequently expressed, most of us feel that the objective—not the only objective, but the chief objective—of genetics research is to understand more completely the manner of inheritance of human characteristics and factors that enter into the manifestation of those characteristics as the human individual develops All our genetics research, whether it is in agriculture, general biology, or whatever field, comes to bear on the problem of human inheritance.

Human genetics is a field of extreme difficulty. Those who have worked in the field are quite aware, and need no reminding, of the fact that the life span of the human

1 The Need for Parental Counseling in Pediatrics

JOSEF WARKANY

A pediatrician interested in prenatal factors responsible for diseases and disorders of childhood has a great deal in common with those interested in human genetics. He believes, of course, in hereditary factors that cause or predispose to human illness and he knows that such factors must always be kept in mind when disorders of prenatal origin are under consideration. He, like the geneticist, is interested in prenatal preventive measures that could reduce the suffering of children and their parents. At the present time parental counseling is among the few preventive measures available for this purpose. However, it is to be expected that the pediatrician's point of view will differ in some respects from that of the geneticist. The two specialties encounter different samples of children, of diseases, and of questions.

There can be no doubt about the great need for parental counseling in the fields of congenital malformations, mental retardation, convulsive disorders, blood dyscrasias, diabetes, and many other diseases. In spite of this need it is not always easy to give satisfactory advice under the circumstances encountered in a pediatric hospital or office. Since I see chiefly children with congenital malformations or mental retardation, I shall illustrate some of the difficulties with examples of these two groups.

being is of such length that it is difficult to get adequate data in terms of generations. This science rests very definitely upon a statistical basis, and we are confronted with various definitions of likelihood of events and levels of probability beset with uncertainties. It is this whole background of scientific knowledge and lack of knowledge, of qualitative information, and uncertainty as to the trend of conclusions which may be applicable to man, that the counselor must keep in mind. For he has essentially a second relationship—that of the physician to his patient—a responsibility for the accuracy of his advice and a responsibility for the results of his advice, in a matter that falls intimately into the reasons why people make certain choices. The responsibility of the adviser here, comes very squarely within the general responsibility of a physician to his patient.

The question of malpractice may never come up in regard to genetics counseling, but it is not to be put aside lightly. It should serve as a reminder, not of a legal responsibility, but of a moral responsibility the counselor has in this very intimate and privileged relationship.

As the discussion extends from purely morphologic aspects of human genetics through more functional aspects, we will probably become more appreciative of the importance of more adequate knowledge; and the significance of the use of this knowledge in human relationships will tend to emerge.

our two cases in one family were also due to recessive inheritance. Some types of recessively inherited chondrodystrophy, such as the Ellis van Creveld syndrome or chondrodystrophia calcificans, are sufficiently distinctive to be separated from the dominant form, but others are not. These cannot always be recognized by clinical examination and may—in the case of the first affected child in the family—lead to erroneous interpretation and counseling. Morquio's disease, when fully developed, can be easily distinguished from classical chondrodystrophy. But even this well-established form may cause difficulties in parental counseling, since typical findings may be absent in early life. A baby born in one of our hospitals was suspected of chondrodystrophy because of disproportionate development of head, trunk, and extremities. The arms and legs appeared short and fat, but X-rays revealed rather slender long bones. The parents were tall and well built and four older siblings were healthy and normal. When the roentgenograms were repeated eight months later, changes in the spine and the hip joints suggested Morquio's disease, which is attributed to a recessive gene. It seemed advisable then to warn the parents that the condition of the youngest child might be repeated in a subsequent child. The warning came late, since the mother was pregnant again. In this case, doubt about the diagnosis prevented a warning in time. Fortunately our omission was rectified by a favorable assortment of the parental germ cells at the right time, and the sixth pregnancy ended happily with the birth of a normal child. I enumerated five systemic bone diseases that may have to be considered in the differential diagnosis of chondrodystrophy and know of others that have puzzled us at times. These forms represent entities of different etiologic origins. Yet chondrodystrophy is treated in some

CHONDRODYSTROPHY

Chondrodystrophy or achondroplasia is, according to the textbooks, a Mendelian dominant with high penetrance, and many pedigrees have been published that support this conception. One can see sometimes one or two children with this disorder in one family in which one parent also has chondrodystrophy. In such a situation a reasonably reliable prognosis can be made for future children in the family and for the future offspring of the affected children. However, the majority of children seen with chondrodystrophy by us do not conform to this simple scheme. First, one sees children with typical chondrodystrophy whose parents are normal and who appear in the pedigree as sporadic cases. Of course, such sporadic appearance does not rule out genetic determination. The sporadic case may be due to a new mutation and the affected child could transmit the disorder to his offspring, each child of the next generation having a 50:50 chance to be affected. It is very unlikely that the normal parents of the sporadic case will have another child with chondrodystrophy, since it is improbable that an identical mutation will occur in the same couple. Yet chondrodystrophy can occur twice in the offspring of parents who appear entirely normal. A child born at one of our hospitals showed short extremities and chondrodystrophy in roentgenograms. The parents and siblings were normal. If this case had been attributed to mutation, this would have largely precluded a repetition of the disorder in this family. However, one year later, a sibling of this child was born showing the same anomalies. Cases of recessive chondrodystrophy have been described, and we assume that

our two cases in one family were also due to recessive inheritance. Some types of recessively inherited chondrodystrophy, such as the Ellis van Creveld syndrome or chondrodystrophia calcificans, are sufficiently distinctive to be separated from the dominant form, but others are not. These cannot always be recognized by clinical examination and may—in the case of the first affected child in the family—lead to erroneous interpretation and counseling. Morquio's disease, when fully developed, can be easily distinguished from classical chondrodystrophy. But even this well-established form may cause difficulties in parental counseling, since typical findings may be absent in early life. A baby born in one of our hospitals was suspected of chondrodystrophy because of disproportionate development of head, trunk, and extremities. The arms and legs appeared short and fat, but X-rays revealed rather slender long bones. The parents were tall and well built and four older siblings were healthy and normal. When the roentgenograms were repeated eight months later, changes in the spine and the hip joints suggested Morquio's disease, which is attributed to a recessive gene. It seemed advisable then to warn the parents that the condition of the youngest child might be repeated in a subsequent child. The warning came late, since the mother was pregnant again. In this case, doubt about the diagnosis prevented a warning in time. Fortunately our omission was rectified by a favorable assortment of the parental germ cells at the right time, and the sixth pregnancy ended happily with the birth of a normal child I enumerated five systemic bone diseases that may have to be considered in the differential diagnosis of chondrodystrophy and know of others that have puzzled us at times. These forms represent entities of different etiologic origins. Yet chondrodystrophy is treated in some

of the texts on genetics or genetic counseling as an etiologic entity permitting uniform genetic prognosis and eugenic advice.

OTHER MALFORMATIONS

It is almost certain that other congenital malformations that we consider as clinical entities are equally heterogeneous in origin. Hydrocephalus, microcephalus, oxycephalus, microphthalmus, cataract, cleft lip, cleft palate, dislocation of the hip, clubfoot, polydactylism, and many others belong in this category. It seems that each of these malformations is merely a symptom that can be the result of different genetic mechanisms or the result of nongenetic prenatal disturbances.

Geneticists have recognized these difficulties of etiologic interpretation and have worked out empiric risk figures for various defects. Although the meaning of risk figures will be discussed by qualified members of the afternoon panel, I must mention here that they cannot be a substitute for specific etiologic diagnosis. The use of risk figures represents a definite step forward in genetic counseling, but it should not be considered a final method. If we admit that many of the malformations encountered are not etiologic entities but merely symptoms, then empiric risk figures derived from pools of heterogeneous cases may be far off when applied to a specific case. It is said, for instance, that cleft palate (without cleft lip) in a child of normal parents represents a 2 per cent risk for a sibling. Does this risk figure also apply to the sibling of a child with cleft palate and mandibulo-facial dysostosis? In the family of one of our cleft palate patients mandibulo-facial dysostosis was inherited like a dominant trait. The chance

for a subsequent child to have mandibulo-facial dysostosis is 50:50. From the literature and our small experience with this syndrome it would appear that cleft palate is not rare in patients with mandibulo-facial dysostosis and that the risk for a subsequent child in this family having cleft palate is greater than 2 per cent. In another case of cleft palate the risk figure for a sibling is probably zero. In this case we can attribute the cleft palate to a chemical substance, aminopterin, which the mother took as an abortive in the second month of pregnancy. Since the mother is not likely to repeat this experiment, the eugenic prognosis for subsequent children should be good. These examples show that cleft palate is not an entity as regards etiology and eugenic prognosis; they indicate that we must try to ascertain the etiologic factors in individual cases and to replace general risk figures by risk figures specific for every single entity. It is obvious that we are not yet able to do this and that we have a great deal to learn about diagnosis, classification, and etiology of congenital malformations before we can give reliable advice in individual cases.

MENTAL RETARDATION

In the field of mental retardation the situation is even more complicated. Gone are the days when feeble-mindedness was attributed to one genetic unit character and when it was discussed as a dominant or a recessive "taint." Several years ago Gibson enumerated about seventy separable types of mental retardation. This must represent an underestimate, since new syndromes are described annually and added to this list. We now think that each of these syndromes or each causative factor must be evaluated separately and that in some of the cases a sound eugenic

prognosis is possible. Mental retardation caused by inborn errors of metabolism represents a facet particularly favored by investigators at the present time. The adverse effects of the metabolic error that causes phenylketonuria, a representative of this group, may be alleviated and even prevented by dietary means. Since this metabolic disorder can be attributed to a single recessive gene, it would lend itself to eugenic counseling if carriers could be discovered by chemical methods. The phenylalanine tolerance test used by Hsia and coworkers showed that, in general, the parents and some of the siblings of the affected children have reduced tolerance for phenylalanine. These findings have been confirmed in other laboratories, but it has been shown also that a few of the parents have normal or nearly normal tolerance curves. This indicates that we are not ready yet to counsel with certainty prospective parents who are possible carriers of this abnormal gene, with the help of this chemical test. Nonetheless, the work on phenylpyruvic oligophrenia has justly aroused great hopes in the field of mental retardation and points the way for future investigations along these lines. At the present time, however, we are not able yet to diagnose and classify the majority of cases of mental retardation, in spite of the many types that have been established as separate entities. If faced with a congenital sporadic case of undetermined origin, we must not consider it uncritically as a "mutation" or as the result of recessive inheritance. We must take into consideration that prenatal infections with viruses or protozoa, prenatal physical or chemical disturbances, interruption of the blood flow or anoxia, hemorrhages or birth traumas can also account for impairment of mental development. Sometimes the history obtained gives no clue, and at other times the history supplies three

or four possible causes of the child's retardation. Needless to say that in either situation the etiology remains obscure and counseling difficult.

PEDIATRICIAN AND CLINIC

I have stressed so far what Fraser has called the "darker side" of heredity counseling, since it seems preferable to emphasize in a symposium like ours what has to be done rather than what has been done. Although the pediatrician interested in prenatal factors may be critical of some oversimplifications expressed by genetic counselors, his attitude should not be considered as negativistic. He recognizes the need for rational parental counseling, but he also recognizes the need for better knowledge in the diagnosis, classification, and causation of disorders for which counsel is sought. He welcomes the existence of clinics where parents can obtain counsel for family planning, but he wonders why such clinics are called "heredity clinics" or why the counseling should be limited to "genetic counseling." It seems there is now general agreement that many of the disorders discussed can be brought on by genetic or nongenetic factors or by both. Why then prejudice the case by calling an advisory clinic a "heredity clinic" although it will deal in many instances with nonhereditary conditions? The pediatrician suggests, therefore, that a "clinic for parental counseling" would be more adequate for the purpose than a "heredity clinic." He suggests that parental counseling should be done by a team that includes geneticists but also pediatricians well versed in the diagnosis, variability, and nosology of the disorders to be evaluated. The team should also contain other specialists who can be consulted in appropriate cases.

Hematologists, virologists, and immunologists could make valuable contributions. I believe that such teams will be research teams for some time to come. For the time being it would seem preferable to have a limited number of clinics with highly qualified staffs drawn from many disciplines rather than to spread the available talent too thin. It should not be too difficult to find pediatricians to join such clinics, since there is more interest in genetic and other prenatal factors among pediatricians today than at any time before.

2 Genetics and Dentistry

CARL J. WITKOP, JR.

The dentist is concerned with three major problems relating to genetics. The first problem concerns the safe use of diagnostic X-rays to minimize any germinal or somatic cell damage. The second problem deals with those inherited factors influencing the normal growth and development of oral structures. The third problem concerns the inherited diseases of the teeth and surrounding structures. It is this last problem that is of interest to the heredity counselors

In some dental diseases inherited factors can be decisive or only contributory to the production of a specific illness. For example, dentinogenesis imperfecta, an inherited defect in the formation of dentin, is produced only when a person is heterozygous for the defective gene. However, variations in the clinical appearance in these teeth are partially ascribable to environmental factors to which these defective teeth are subjected after eruption into the oral cavity. On the other hand, the work of Hunt (2) on dental caries in rats indicates that hereditary factors such as anatomical variations in tooth form (5) affect the caries susceptibility but that environmental factors are most likely the major etiological agents in this disease (3). It is only in the former instance, where the disease is primarily genetically determined, that the heredity counselor can

TABLE 1. HEREDITARY ORAL DISEASES

Oral disease	*Mode of inheritance* D=Dominant R=Recessive S=Sex-linked IS=Intermediate sex-linked	*Accuracy of genetic prognosis* ***=accurate **=approximate *=questionable
HERITABLE DEFECTS IN DENTITION WITHOUT GENERALIZED DEFECTS		
Hypoplasia of enamel	*SD*	**
Hypocalcification of enamel	*D*	***
Hypomaturation of enamel	*SR*	***
Pigmented hypomaturation of enamel	*R*	*
Local hypoplasia of enamel	*D* (with incomp. penetrance)	**
Dentin dysplasia	*D*	***
Dentinogenesis imperfecta	*D*	***
Missing or peg laterals	*D*	***
Missing maxillary incisors and cuspids	*D* or *R*	**
Missing premolars	*D*	**
Missing third molars	*D*	**
Gigantism of maxillary central incisors	*D*	**
Fused primary mandibular incisors	*D*?	***
Familial dentigerous cysts	*D*	**
HERITABLE DEFECTS IN DENTITION WITH GENERALIZED DEFECTS		
Dentinogenesis imperfecta with osteogenesis imperfecta	*D*	**
Enamel hypoplasia in vitamin D resistant rickets	*D* (irregularly) (*SD*)	**
Enamel hypoplasia with epidermolysis bullosa dystrophia	*R*	**
Local hypoplasia of enamel with Fanconi syndrome	*R*?	*

TABLE 1. (*Continued*)

Oral disease	*Mode of inheritance* D=Dominant R=Recessive S=Sex-linked IS=Intermediate sex-linked	*Accuracy of genetic prognosis* ***=accurate **=approximate *=questionable
Missing teeth with ectodermal dysplasia	IS or D	**
Missing premolars with premature whitening of hair	D	***
Missing lateral incisors with ptosis of eyelid	D	**
Retarded eruption with cleido-cranial dysostosis	D	**
HERITABLE DEFECTS OF ORAL STRUCTURES WITHOUT GENERALIZED DEFECTS		
Ankyloglossia	D	**
Elephantiasis gingivae	D	**
Harelip and harelip with cleft palate	R?	*
HERITABLE DEFECTS OF ORAL STRUCTURES WITH GENERALIZED DISEASES		
Gangrenous stomatitis with acatalasemia	R	**
Periodontitis with agammaglobulinemia	SR	**
Periodontitis and osteoporosis of jaw bones with thalassemia major	R	***
Alveolar bone changes in sickle cell disease	R	***
Gingival and postoperative hemorrhage in hemophilia and Christmas disease	SR	***
Mucosal telangiectasia in hemorrhagic telangiectasia (Osler)	D	**
Facial angiomatosis with Sturge-Weber's disease	D (irregular)	*

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Hypoplasia of enamel	SD	**
Hypocalcification of enamel	D	***
Hypomaturation of enamel	SR	***
Pigmented hypomaturation of enamel	R	*
Local hypoplasia of enamel	D (with incomp. penetrance)	**
Dentin dysplasia	D	***
Dentinogenesis imperfecta	D	***
Missing or peg laterals	D	***
Missing maxillary incisors and cuspids	D or R	**
Missing premolars	D	**
Missing third molars	D	**
Gigantism of maxillary central incisors	D	**
Fused primary mandibular incisors	D?	***
Familial dentigerous cysts	D	**
HERITABLE DEFECTS IN DENTITION WITH GENERALIZED DEFECTS		
Dentinogenesis imperfecta with osteogenesis imperfecta	D	**
Enamel hypoplasia in vitamin D resistant rickets	D (irregularly) (SD)	**
Enamel hypoplasia with epidermolysis bullosa dystrophia	R	**
Local hypoplasia of enamel with Fanconi syndrome	R?	*

make relatively accurate predictions at this time.

INHERITED DENTAL DISEASES

The intrinsic diseases of dental significance can affect oral structures only, or they can be present as oral manifestations of generalized hereditary disease. Table 1 illustrates these defects. Only those conditions that have been fairly well established as genetic in origin have been included. It is to be remembered that some of these diseases may be mimicked by nongenetic phenocopies. A few of these defects will be discussed in detail.

Heritable Defects in Dentition Without Generalized Defects

In order to determine the prevalence, inheritance and classification of hereditary enamel and dentin defects, a survey of 96,471 children was conducted in the State of Michigan (15). There are at least five distinct inherited defects in enamel. All teeth in both dentitions are affected except in local hypoplasia. Extensive clinical studies at the National Institutes of Health failed to reveal any other consistent physical or metabolic abnormality in patients affected with these conditions. All inherited enamel defects taken together occurred once in 14,000 to 16,000 children.

Two or three of the conditions are fairly well known and can be accurately diagnosed by an oral pathologist, but to differentiate among some of them is very difficult. As a general rule, if both dentitions are affected the condition is usually genetically determined. I have seen conditions where this was not so, but most dentists do not know what these conditions are. They usually attribute the de-

TABLE 1 (*Continued*)

Oral disease	*Mode of inheritance* D=Dominant R=Recessive S=Sex-linked IS=Intermediate sex-linked	*Accuracy of genetic prognosis* ***=accurate **=approximate *=questionable
Oral hematomas with Ehlers-Danlos syndrome	D	**
Facial deformity in gargoylism	R (RS)	**
Facial deformity with mandibulo-facial dysostosis (Franceschetti)	D (irregular)	**
Facial deformity with cranio-facial dysostosis (Crouzon)	D (irregular)	**
Micrognathia with Pierre Robin syndrome	R (incomp. dom.)	*
Hypoplasia of maxilla with achondroplasia	D	**
Multilocular cystic fibrous dysplasia of the jaws and face (Jones)	D	***
Osteosclerosis in Albers-Schonberg disease	D (irregular)	**
Hyperostosis of jaws in generalized hyperostotic bone disease (Witkop)	R	***
Hypercementosis and bone changes in osteitis deformans (Paget)	D (incomp.)	*
Neurofibroma and pigmentation in neurofibromatosis (von Recklinghausen)	D	**
Circum-oral pigmentation with gastrointestinal polyposis (Peutz-Jegher)	D	**
Facial pigmentation and carcinomas of lip in xeroderma pigmentosum	ISR or R	**
Gingival and lingual amyloid deposits in familial amyloidosis	D	**
White spongy nevus of mucous membranes	D	***

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fects to a fever in childhood or to some infectious disease occurring in the early period of life. Fevers and severe vitamin deficiencies early in life do cause defects that look similar to local hypoplasia, but there is nothing I have ever seen that causes dentin dysplasia, dentinogenesis imperfecta, hypocalcification of enamel, or hypoplasia of enamel where all the enamel is very thin, that was other than a genetic defect.

1. *Hypoplasia of Enamel*

The enamel is about one fourth the thickness of normal enamel, has a granular surface, and is very hard. The teeth are light brown in color and are usually separated at the contact points. Schulze (11) reported that this condition is inherited as a sex-linked dominant in five extensive pedigrees.

2. *Hypocalcification of Enamel*

This condition is the one commonly referred to as amelogenesis imperfecta (13). The enamel is dull brown in color and very soft with a rough surface. It can be scraped from the underlying normal dentin by a sharp instrument. The enamel persists only a short time after the teeth erupt. This condition is inherited as an autosomal dominant trait.

3. *Hypomaturation of Enamel*

In this condition the teeth are an opaque white when they first erupt, but they turn light brown later. Calcium salts are deposited in the matrix but do not mature to the hard apatite crystal. The tip of an explorer can be forced into the surface of the teeth with firm pressure. A collar of normal-appearing enamel may be present at the

cervical portion of the crown. This condition is transmitted as a sex-linked recessive trait.

4. *Pigmented Hypomaturation of Enamel*

The enamel is of normal thickness but is not as hard as normal enamel. The surface is shiny, agar brown in color, with a brown pigment extending throughout the thickness of the enamel. Histochemical stains indicate that this is not blood pigment. This condition is probably inherited as an autosomal recessive trait.

5. *Local Hypoplasia of Enamel*

Only the primary teeth may be affected in this condition. Brown pitted or lined hypoplastic areas occur mostly on the incisors and premolar teeth. All teeth may show hypoplasia. There is wide variation in the number of teeth affected in individuals from the same kindred. In two instances the trait was transmitted by persons with normal-appearing teeth, once by a male and once by a female. This is inherited as an autosomal dominant trait.

In addition to these five conditions there are probably at least two more enamel defects that are hereditary in nature. We have investigated reports that dentists in a community see what is at first called fluorosis after 1 part per million of sodium fluoride is added to the water supply. On examining these children, we find as high as 15 per cent of them have some variation in the color of the teeth —usually a yellow. This is not fluorosis. One explanation may be that there are several forms of genetically controlled normal variants of enamel similar to the variants of hemoglobin. This would offer a possible explanation for the inconsistent results obtained in many attempts to determine the chemical and structural composition of enamel,

and in turn account for the differences in D M F (*Decayed, Missing, and Filled,* a standard of dental caries experience) rates seen in members of the same family subjected to similar environmental influences.

Two hereditary defects of dentin were found in the survey: dentin dysplasia and dentinogenesis imperfecta. These two conditions have certain similarities and are often confused because both lack root canals and pulp chambers. They are, however, entirely separate entities.

Dentin dysplasia is also known as rootless teeth. It is frequently misdiagnosed as dentinogenesis imperfecta (9). The crowns are well formed and nearly normal in color. The roots may be absent, blunted, or may be only short spicules. A characteristic chevron or half-moon-shaped remnant of pulp chamber is seen in the x-ray of these teeth. Root canals are usually absent. Many teeth show large radiolucent areas around the apices of the root. The condition is transmitted as an autosomal dominant trait.

Dentinogenesis imperfecta has been called opalescent dentin, Capdepont's teeth, odontogenesis imperfecta, hereditary brown teeth, and shell teeth. Many of these names originated because one or two of the many variations this condition shows were emphasized by the author as points of differential diagnosis. We have seen some 350 cases of this condition in extensive kindreds. We also have examined as many as 140 affected individuals in the same kindred and have seen all the variations ascribed to separate entities.

Dentinogenesis imperfecta occurs in the general population of Michigan about once in 8,000 individuals. In certain isolated populations the frequency is much higher (14). The teeth vary from an opalescent blue to an amber brown in color. The enamel may fracture from the defective

dentin soon after eruption or may remain intact on the crowns of the teeth throughout life. The enamel may be normal or hypoplastic. The crowns are usually bulbous in shape and the roots short. The pulp chambers are usually absent but may be normal in size or even very large, resulting in a shell tooth (8, 14). This condition is transmitted as an autosomal dominant trait with nearly complete penetrance.

The homozygous state for this condition was not seen. This trait is so uncommon in the population that a mating that would give you a homozygous offspring would be extremely rare. It was only in an isolated population, where people were forced by social and religious factors to marry within their own kind, that a situation like this did turn up with any frequency.

Two such marriages have occurred where both parents had dentinogenesis imperfecta. One was in past generations where we cannot obtain good data on the mother's pregnancies, but in this particular instance, where we do have information, the mother had seven pregnancies with only two viable offspring. Both children appeared to be heterozygous for this condition. The other five pregnancies terminated in abortions between the second and fifth month of gestation. The woman had been examined repeatedly after each miscarriage. These examinations did not reveal a specific cause of the miscarriages. Unfortunately none of the fetuses was examined microscopically. The homozygous state of these genes may be lethal.

Linkage studies were made between dentinogenesis imperfecta and phenylthiocarbamide taste testing and secretor factor in saliva. In general, the same sibships were used for both the saliva and the taste testing. The results of the paired-sib analysis are presented in Table 2. It

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trait as do blue sclerae and otosclerosis—the other manifestations of the fragile bone disease. Dentinogenesis imperfecta is found in familial cases of osteogenesis imperfecta and also in those apparently sporadic cases in which no affected predecessor can be detected. In several kindreds the tooth defect has proved to be a more reliable indication of affected individuals than blue sclerae. In one such kindred the blue sclerae were absent, but the dominant inheritance of the trait could be traced through the members with defective teeth for three generations. The combination of fragile bones, dentinogenesis imperfecta and blue sclerae then appeared in our propositus and three first cousins.

It is not known whether dentinogenesis imperfecta, occurring as a separate entity, and dentinogenesis imperfecta with osteogenesis imperfecta are exactly the same condition (9). Schulze (11) claims that there are microscopic differences. However, there are a great number of similarities between these two conditions. There are also similarities between the tooth defect and the bone defect.

McKusick (6) states that there is a bell-shaped curve of severity of osteogenesis imperfecta and that the separation of the congenita and tarda forms is somewhat artificial as both forms may occur in the same family. A like situation exists for dentinogenesis imperfecta, both with and without bone disease, so that both severe and mild forms of tooth defect may occur in the same kindred. In our cases the teeth erupt early in the more severely affected individuals. However, Pindborg (7) reports delayed eruption of the teeth. We have seen the eruption of permanent teeth as early as three years of age. There is another similarity to the congenita and tarda types of bone defect in that the

TABLE 2. LINKAGE DATA

Paired sib method

Dentinogenesis imperfecta—PTC

LL	LU	UL	UU	Total
28	13	10	24	75

$x^2 = 11.24$ $df = 1$ $P < .001$

Dentinogenesis imperfecta—secretor factor

LL	LU	UL	UU	Total
19	19	11	11	60

$x^2 = 0$

appears that there is probably linkage between dentinogenesis imperfecta and phenylthiocarbamide taste trait.

Congenitally hereditary missing teeth may show some variation in the number of teeth missing, depending on whether the person is heterozygous or homozygous for the gene involved (4). Some of these genes are relatively common in the population. Grahnen (1) reported prevalence of 5 to 6 per cent of missing teeth, excluding third molars, in Swedish populations.

Other conditions related to the spacing and shape of the teeth have been shown to be genetically determined. Shovel-shaped incisors and large maxillary incisors seem to be inherited as dominant traits.

HERITABLE DEFECTS IN DENTITION WITH GENERALIZED DEFECTS

Dentinogenesis imperfecta sometimes occurs as part of the osteogenesis imperfecta syndrome (12). *Dentinogenesis imperfecta* may also occur as an independent hereditary

lower incisor teeth when the mouth was opened to its fullest extent. The mode of inheritance of this condition is difficult to determine in most families, because in many new-born infants the frenum is cut, if it appears to interfere with tongue function.

HERITABLE DEFECTS OF ORAL STRUCTURES WITH GENERALIZED DEFECTS

The Ehlers-Danlos syndrome is of particular interest to dentists because of the frequency with which these patients have post-operative complications of massive edema and swelling. This condition has been neglected in the dental literature, and very few descriptions and reports of this disease appear anywhere (6). Yet, it is perhaps one of the most common connective tissue diseases encountered in southern Maryland among a group selected as a control for our inbred population studies. Biochemical studies on these patients have failed to reveal any defect in hydroxyproline metabolism.

White spongy nevus of mucous membranes is of dental interest because it is sometimes misdiagnosed as precancerous leukoplakia. It has frequently been described as an oral lesion only but usually involves vaginal mucosa also (16).

A RESEARCH PROGRAM IN HEREDITARY DISEASES

In 1955, we examined three individuals with dentinogenesis imperfecta who claimed vague relationship with one another. In trying to determine the exact relationship by kindred chartings, it soon became apparent that we were dealing with a most unusual family. In tracing all sides of all affected sibships we found that only eight sur-

teeth which erupt first are the most severely affected. The primary teeth, permanent first molars, and incisors are usually very defective. The permanent cuspids and second molars, which erupt at 11 and 12 years of age, are less severely affected. There is apparently a tendency toward normal dentin formation in the teeth that develop later. The cuspid and second molar begin their development at about two to three years of age; therefore, the lessened severity of the defect in these teeth cannot be ascribed to hormonal changes in puberty.

In sections of bone from cases of osteogenesis imperfecta there is found a basophilic, PAS (periodic acid Schiff), positive substance not present in normal bone (6). A similar substance is found in teeth affected with dentinogenesis imperfecta with or without osteogenesis imperfecta.

Ectodermal dysplasia is a condition in which the ectodermal portions of the tooth germs fail to develop properly, resulting in absence of all or some of the teeth. Males are more severely affected than females. This condition is classified as an intermediate sex-linked trait, because females who carry this gene usually show absence of at least one or two teeth or other stigmata of this disease (10).

Heritable Defects of Oral Structures Without Generalized Defects

Ankyloglossia or tongue-tie appears to be dominantly inherited. We have been studying this condition and its effects on speech in a population residing in southern Maryland. We found during our dental and medical studies that 50 persons of the 731 examined had a prominent lingual frenum that prevented them from raising the tip of the tongue beyond a point midway between the upper and

tion. The usual laboratory tests are within normal limits. There are no hematological changes. There is no history of fractures in these cases. We are calling this syndrome recessive generalized cortical hyperostosis.

This population offers the opportunity to find matings rare in human material. In diseases where the genetic factors are only contributory, it may be possible further to define the role heredity plays in their etiology. For example, after examining the dental condition of 780 patients, it was determined that the D M F rates and the lactobacillus counts (a bacterial test of dental caries activity) were similar to those in communities with 1 part per million of sodium fluoride in the water supply. In the communities with fluoride in the water supply these rates are about 60 per cent lower than communities without fluoride. In Prince Georges and Charles Counties, Maryland, where this isolate resides, the fluoride content varied from .02 to .08 part per million—far below that required to produce a decrease in caries activity.

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names appeared, which were repeated with monotonous frequency. Other defects of a hereditary nature were found in these families, which included an ear defect, albinism, polycystic kidneys, deaf-mutism and Brailsford-Marquio's disease. Further investigation disclosed that we were dealing with a population isolate. This isolate comprises about 5,000 individuals of mixed racial ancestry who did not consider themselves Negro and were not admitted into the white marriage patterns of the community. We are now conducting extensive research on the social, medical, and dental aspects of this group. Because the in-marriage pattern has persisted in this population since before 1760, many recessive characteristics appear in the homozygous state. For example, 57 albinos have appeared in this population; 49 are living today. Seven hundred and thirty-one unselected individuals were examined this summer. Of this number 104 had positive sickling tests, including both SA and SS hemoglobin patterns. A rare peculiar form of recessive generalized hyperostotic bone disease was found in five members of one sibship. This disease has probably not been described before. All bones are affected. The first symptoms appear at about four to five years of age with a swelling, always on the right side of the jaw, accompanied by a seventh nerve paralysis that persists after the swelling subsides. Gradually both sides of the face are involved. Loss of hearing begins at about six to nine years of age and becomes progressively worse. A progressive retinal atrophy and exophthalmos develops. The base of the skull is involved in the hyperostotic process early, and eventually the jaws and facial bones show the hyperostotic changes of leontiasis ossea. The long bones show tremendous cortical thickening. They are considerably larger than normal but retain their normal configura-

3 Genetics in Public Health Nursing

HAZEL R. DYSON,
CARL J. WITKOP, JR., AND
SHIRLEY S. BUTTERS

The functions of the public health nurse have been defined in many ways. At a recent meeting of the American Public Health Association much time was devoted to the discussion of recent trends in public health thinking (10) and the role to be played by the nurse in the solution of the health problems now confronting us (9). Intrinsic disease is assuming more importance in these problems as at least 2 per cent of the general population has serious genetic illness (11). Fleck (3), in defining the duties of public health nurses, states, "They function as the eyes and ears of all health services," and are in "a strategic position to collect epidemiologic data and identify relevant factors or help eliminate irrelevant ones." In order to carry out these assigned functions the public health nurse will benefit by a knowledge of hereditary disease, the basic modes of inheritance, and the social factors in the community that may influence the prevalence and distribution of hereditary disease This knowledge can be useful in case finding, referral planning, and locating situations in the population with potential research value.

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has not been definitely established, history was obtained from the initial patients about the occurrence of diabetes, or the symptoms of diabetes, among their relatives. All siblings of any person with a suspicious history were asked to report to the clinic for urine or glucose tolerance tests. At least one additional case of this disease usually was found in the families of the initial patients.

During the early stages of a dental examination program it was noted that some of the children were tongue-tied. The teachers in the community reported that a considerable number of these children also had speech difficulties. It is not known whether the speech disorders were the result of the tongue defect, but an examination of the siblings and parents of these children showed a high prevalence of tongue-tie. These cases were referred to the speech therapist for evaluation and further study.

REFERRAL PLANNING

Kemp (8) states, "It is important for the social and public health authorities to know the number of people in their communities, who, because of hereditary disease, are incapacitated and must be given social relief, to be treated, or to be placed in hospitals or institutions." A knowledge of which diseases are genetically determined is most useful in planning public health and public assistance programs because patients with these diseases usually require long-term treatment or social aid.

In one community six families have come to our attention where both parents are heterozygous for the sickle cell gene. Thirteen children in these families have been hospitalized for varying lengths of time because of this illness. Owing to the frequent need for transfusions, all

CASE FINDING

A knowledge of inheritance patterns of disease may be helpful in a screening program. If an individual is found to have an inherited disease, examination of other members of the kindred may reveal additional examples of this disease, thus increasing the effectiveness of the screening procedure. If, for example, the mode of inheritance is recessive, at least the siblings of the initial case should be examined. If the mode of inheritance is dominant, the nurse can trace the affected individuals by history and home visits and help to establish the sibships that should be examined. These procedures can be modified for the sex-linked traits.

We have used this knowledge in an eye-screening program for chronic simple glaucoma. Studies on this disease have shown that there is an increased incidence of glaucoma among close relatives of affected individuals (14) and that it is usually inherited as an autosomal dominant trait (12). Two patients with chronic glaucoma were found during one of our routine eye surveys. The nurse then obtained a family history of eye disease, helped to *establish the sibships in which glaucoma was most likely* to occur, and arranged to have these people examined. Five additional cases of frank glaucoma and one glaucoma suspect were found. Two of these patients were discovered before they were aware of any eye trouble. By finding glaucoma in its incipient stages, it may be more susceptible to treatment and the damaging effects of prolonged intraocular pressure avoided.

A similar procedure has been utilized in the detection of diabetes. Because the mode of inheritance of this disease

emotional and psychological problems (7). A failure to understand this fact may lead to tragic results. The public health nurse, with knowledge of genetics, will recognize the need for special guidance in these situations. If a heredity counselor is available, she may refer the family to him for advice. In most communities this service is not available, so the family is referred to private physicians or hospitals for guidance in these matters.

SOCIAL FACTORS IN THE COMMUNITY INFLUENCING THE PREVALENCE OR DISTRIBUTION OF INTRINSIC DISEASE

The public health nurse is in an ideal situation to observe the factors in her community that influence the prevalence or distribution of intrinsic disease. The longer she works in an area, the more familiar she becomes with a large number of family relationships, family dynamics, and the existence of particular sects or subgroups. These factors will be more apparent in a rural or suburban setting than in larger centers of population. Most hereditary disease is familial. In the community, therefore, the marriage patterns of the population will influence the distribution and occasionally the prevalence of intrinsic disease. Recessive traits usually are shown more frequently in marriages of near kin. As a result, factors that tend to limit the number of individuals among whom a person can select a mate will frequently increase the number of kin marriages in a community

Certain generalities can be stated concerning these factors. If large metropolitan areas are disregarded, the following statements will generally hold true. Marriages

these families have been forced to call upon public facilities for medical and social aid. Several of these families have more than one member affected with sickle cell disease. Fortunately, we have been able to refer these patients to a research facility or teaching hospital in the community for care. In such instances, where several members of a family are affected with a hereditary disease requiring long-term treatment, it is advantageous to make arrangements with one facility for care of all the affected members of the family. This eliminates the need for repeated referrals. Such an arrangement is particularly desirable in cases of sickle cell disease, where the onset of a sickling crisis may be a medical emergency requiring immediate hospitalization.

In certain counties in the United States, the population is divided into more or less isolated social segments; therefore, marriage between persons with common ancestry is fairly frequent (1). Many of these counties have a considerable load of hereditary disease that requires an expenditure of public funds. Hereditary conjunctivitis, leading to blindness, occurs frequently in Halifax County, North Carolina. Many of the affected individuals were drawn from one group of families. At least thirty residents of this county have required treatment for this condition during the past year. The use of public facilities and the expenditure of public funds contributed to the treatment of these patients.

The public health nurse may be the first professional person to approach a family in which hereditary disease exists. She may also be the first person to whom the family turns for information concerning hereditary illness. Because of the nature of hereditary disease and its transmission through the germ plasm, it frequently carries many

such groups. In the latter some striking genetic differences from the general population of approximately the *same* racial stock have been noted (4).

Certain racial groups have formed primarily in the eastern part of the United States and are termed racial isolates. Some twenty-six of these groups have been identified (15, 16). Their marriage patterns are limited because they are outside the usual racial classifications of white, Negro, Indian, or Oriental. As a result these people have married within only a few families for generations and show a very high prevalence of intrinsic disease (6).

In no county does the isolate group comprise more than 10 per cent of the population except in certain areas of the Carolinas, where they may be as high as 70 per cent. Some groups live near counseling services, especially those near Bowman Gray Medical School, Johns Hopkins University, Ohio State University, and the University of Pennsylvania. For the most part, however, the isolates are fairly remote from any counseling service, and in many, the people are not of an economic or cultural level to accept the advice that might be given them.

PUBLIC HEALTH NURSES IN A RESEARCH PROGRAM

The Human Genetics Section of the National Institute of Dental Research has been conducting an investigation into the dental, medical, genetic, and social aspects of a population isolate residing in Maryland (16). This group consists of about 5,000 individuals of Caucasian, Negro, and American Indian ancestry, who have been regarded as a separate racial class since before 1760. These people were not accepted into the white community and did not con-

between persons with common ancestors will occur more frequently, the older the community, the smaller the community, the more stable the community as far as immigration and emigration are concerned, and the more geographically isolated the community (2). Thus, in areas meeting the above criteria, recessive genetic diseases may emerge as the chances for marriages leading to homozygous offspring are increased. It does not hold true that all communities where the above conditions obtain will show this increase because there may not be deleterious recessive genes in the common ancestors. Dominant genetic traits may be prevalent in some of our older stable communities, provided they were introduced into the population by early residents of the area. Polydactylism in the newborn is occasionally seen in Charles County, Maryland; however, in adjacent Calvert County, extra digits at birth are a common occurrence.

When marriage patterns become very restrictive in any area or for a given group of people, and these restricted patterns are continued over a period of several generations, an isolate results (13). In an isolate there is a chance that any two individuals who marry are related through some common ancestor, and, therefore, the possibility exists that they share common genetic material. Isolates are not uncommon in this country. As examples, there are numerous small religious groups that permit marriages only within that religion. These groups remain relatively small and retain approximately the same genetic composition, as only a few new converts are admitted each generation. Thus, after a time, nearly everyone is related to everyone else. The Hutterites of the western United States and Canada and the Dunkers of Pennsylvania are examples of

such groups. In the latter some striking genetic differences from the general population of approximately the same racial stock have been noted (4).

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sider themselves Negroes. As a result, they marry, for the most part, within fourteen surnames, of which only seven are common. The purpose of this study is to find all the hereditary disease present in this population.

This study is divided into three phases. In phase one, public health nurses obtain genetic, social, and medical histories from each individual by interviewing all persons over sixteen years of age. They arrange these data by family groups and by sibships. In phase two, each individual receives a medical, dental and eye examination in the field. Blood, urine and saliva specimens are obtained for various tests. In phase three, selected individuals are brought into the Clinical Center for detailed studies. Analyses of these data are to be made by I.B.M. tabulation.

Public health nurses were selected to participate in this investigation because their professional training and field experience could be utilized in all phases of the study. They had sufficient knowledge of the signs and symptoms of disease to obtain an adequate preliminary medical and dental history. They could utilize their clinical training during the field examinations and hospital studies. One nurse had worked with these people previously, had established a good rapport with the families, and provided the necessary *entrée* into the group.

The nurses selected to participate in this program were given a four-week training course at the University of Michigan and the National Institutes of Health. This program included introductory genetics, medical genetics, elementary statistics, and interviewing techniques. This program was followed with a two-month period in the field under the supervision of an experienced investigator. The study required that the nurses obtain a kindred chart, a household census, and a medical and social history of

each family. The medical history was taken in the form of a questionnaire covering 158 items. Because all the hereditary diseases of the people were not known at the beginning of the study, it was necessary that both the medical and the social interview be as open as possible to allow additional information to be obtained from the informant and recorded on the questionnaire. The results of each pregnancy were recorded.

INTERVIEWING

It soon became apparent that there were considerable variations in the economic and educational levels, even among siblings, in this group. The nurse endeavored to obtain the initial kindred and census data from the most responsible and best-informed person in the family group. This method of approach was of considerable importance as the attitude of the initial contact often determined the degree of co-operation she received from the rest of the family. The objectives of the study and the method of recording the information in code to protect the identity of the family were explained. Each member of the family over sixteen years of age was interviewed separately, if possible. The information received from one individual was checked against that obtained from the siblings and parents. In this manner we frequently were able to obtain fairly reliable information on stillbirths, miscarriages, and illegitimacy.

The social information was then verified from birth and marriage records obtained by the sociologist. The verified data were given to the geneticist who is constructing a kindred chart of the entire group. One of our most difficult problems is to identify individuals, many with the same

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HEREDITY COUNSELING PROBLEMS

We would like to raise several questions for discussion at this symposium concerning heredity counseling in isolate populations. Since the initiation of this study the subjects of this investigation have become aware that their hereditary diseases are somewhat unusual. Many questions are put to us by these people, the local physicians, and the public health authorities. We have also found the isolate to have confidence in the group conducting the examinations.

In one family the parents are at least third cousins. The mother has an external ear defect and dentinogenesis imperfecta. She has had three children and is expecting a fourth. All three children have dentinogenesis imperfecta. Two have defects of the external ear, which is transmitted as a dominant trait. Two are also deaf-mutes and require special schooling. Two of the father's maternal uncles are also deaf-mutes. The county health officials ask us if the mother should have more children.

A thirty-eight-year-old woman in her eighteenth pregnancy asks our opinion about sterilization. Two of her children are albinos. The family is barely able to subsist on an income of $42.00 a week. The family physician recommends sterilization, but this conflicts with her religious teachings.

A mother with thirteen children decries the fact that six of them must go through life with brown stubs in place of teeth.

In sharp contrast to the above situations, an albino woman confided to the nurse that her greatest desire was to have an albino child, but that matings with at least three

given name, in a group with only fourteen surnames. The magnitude of this problem can be imagined when it is realized that in a 104-year period, in one parish, 129 family "A" men married a group member in all but ten instances. Of these marriages, 40 per cent were to family "A" women and 20 per cent to family "B" women. Thus 92 per cent of the marriages were endogamous. In this same 104-year period, 17 per cent of the group marriages required ecclesiastical dispensation for relationship (5). The large size of the families also makes it difficult to trace all lines of relationship. A direct estimate of family size from our sibship schedules indicates that the average woman had about 5.7 offspring between the years 1900 and 1950. These sibships ranged in size from none to twenty-two individuals.

FIELD EXAMINATIONS

During the summer months field examinations were conducted. Two trailers were equipped for medical examinations and one for dental examinations. It was the responsibility of the nurses to equip and maintain all examination facilities. Six recorders were trained and supervised by the nurses. It was the duty of the nurses to make appointments for entire family groups, collect blood, urine, and saliva samples, and administer phenylthiocarbamide taste tests.

The results of these investigations show a large amount of hereditary disease among these people. The three most common intrinsic diseases found to date are dentinogenesis imperfecta, 171 cases; sickle-cell trait or disease, 118 cases; and albinism, 55 cases. Twenty-two other inherited conditions or conditions in which genetic factors are suspected occur in this group.

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spouses had produced only normal or deaf-mute children.

The questions we would like to raise are: Does the heredity counselor present the facts about the risks involved and let the individuals decide upon a course of action, or does he recommend that certain measures be taken? What advice is to be given to young people contemplating marriage within an isolate group? The answers to these questions involve counseling of an entire population rather than individuals when the facts of social and religious restrictions make it difficult to find an acceptable marriage partner outside the group. At least 77,000 people in this country are members of such racial isolates and are faced with this problem.

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glycogen disease of the heart, progressive muscular dystrophy, myotonic dystrophy, and Friedreich's ataxia. But we will confine our remarks to the Big Four.

For many reasons, the genetic factor is extraordinarily difficult to study in these disorders. Probably in no other major category of disease is multifactorial causation so complex. The multiple factors are both environmental and genetic. Obviously to state that genetic factors of some significance are involved in rheumatic fever does not deny the role of the streptococcus. To say that heredity is significant in atherosclerosis does not deny the significance of diet. To point out a genetic factor in congenital heart disease does not exclude the important role of the intrauterine environment, e.g., with reference to maternal infection.

The two biggest of the Big Four, hypertension and atherosclerosis, are not independent operators. Each potentiates the other and study of one must take the other into consideration.

Rheumatic Fever

In the case of rheumatic fever, heredity presumably determines why only certain of those individuals exposed to the appropriate streptococcus develop the disease. Were there a method for identifying the genetically susceptible individual, it might be possible to provide more economic and effective prophylaxis, especially to individuals in high-risk environmental situations such as barrack life. It would be of great interest, both theoretical and practical, to know what distinguishes the "rheumatophilic" individual from the general population and to know the mechanism of the genetic enhancement of susceptibility to rheumatic fever.

4 Genetics in Relation to Cardiovascular Diseases

VICTOR A. McKUSICK

In 1745 Lancisi remarked on the occurrence of aneurism of the heart, his term for cardiomegaly, in male members of three generations. Over a century earlier Peter Forestus had described a familial incidence of cerebral hemorrhage. In his *magnum opus*, Morgaeni described the cerebral hemorrhage of one Zani whose father had likewise died of "apoplexy." In moments of gloom, I think we are very little removed from the position of these writers of two and three centuries ago: Heart diseases tend to "run in families." My charge in this symposium, as I interpret it, is to survey in bird's-eye manner how much further ahead, if at all, we are.

THE BIG FOUR

Probably all would agree that some genetic influence is involved in the pathogenesis of all four of the major varieties of cardiovascular disease: congenital malformation of the cardiovascular system, rheumatic fever, hypertension, and atherosclerosis, including coronary artery disease. Clearer operation of genetic factors is seen in the rare varieties of heart involvement occurring as part of tuberous sclerosis, the syndromes of Marfan and of Hurler,

4. There is some increased concordance in monozygotic twins as compared with dizygotic.

5. There is an increased incidence among the first cousins of the probands.

6. About one fifth of the cases, regardless of the specific type of the cardiovascular malformation, show other congenital malformations.

There is not complete agreement as to how much intrafamilial similarity there is in the variety of malformation.

Two general observations may be made. It is essential to consider the precise type of malformation separately. The genetic factor appears to be less important in some malformations, such as simple ventricular septal defect, than in others, such as pure pulmonary stenosis or patent ductus arteriosus. Intrafamilial similarities are more striking for some. Some malformations, specifically coarctation and

TABLE 3. Congenital Malformations Produced with Teratogenic Agents

CROSS-BEAK IN CHICKENS		
Breed	*Sporadic incidence*	*After 40 mgm/egg ethyl carbamate*
White Leghorn	0 20%	6 8%
Black Minorca	1.63%	25.4%
HARELIP AND CLEFT PALATE IN MICE		
Strain	*Sporadic incidence*	*After cortisone to mother*
1	5 0%	100%
2	0 2%	18.7%

After Landauer.

Although there are data that appear to leave no doubt of a genetic factor in this disease, rheumatic fever illustrates how easy it is to misinterpret certain observations as indicating a genetic basis. The idea emanated from Boston a few decades ago that persons with red hair, fair skin, freckles, and blue eyes are more susceptible to rheumatic fever, presumably because of genetic constitution. This conclusion was probably based on the character of the Boston population at that time. Beginning in the middle of the last century, large numbers of Irish families immigrated. They lived under crowded and undernourished circumstances ideal for the development of rheumatic fever. Later as Irish immigration waned and the Irish already in Boston became more prosperous, immigration from southern Italy and Sicily increased. Families of Italian origin took over the cold-water flats, crowded living facilities, and pick-and-shovel work. *Pari passu* the complexion of rheumatic fever in Boston changed, quite literally.

Congenital Malformations

In recent years several excellent studies on the genetics of congenital malformations of the heart and great vessels have established the following generalizations:

1. An aggregation of cases in sibships occurs such that the incidence of cases among the sibs of probands is on the average increased 10 to 15 times over that in the general population and in the case of some types of malformation, 40 times.
2. The consanguinity rate is increased in the parents.
3. Congenital malformations of the heart occur rarely in two successive generations.

tion to atherosclerosis may operate through many avenues. Diabetes with its associated defect of lipid metabolism is

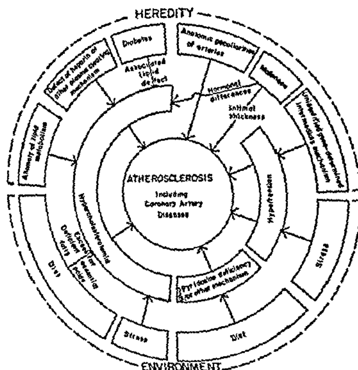


FIG. 1. Complex multifactorial causation in atherosclerosis. Some would include also—on the environment side of the wheel—smoking and degree of physical activity. These are factors that may influence serum cholesterol and may influence the incidence of complications of atherosclerosis.

one mechanism or perhaps a cluster of genetic mechanisms. Parenthetically, diabetes, per se exceedingly difficult of genetic analysis, illustrates how much more complex is the problem of atherosclerosis, to which it is but one contributing factor.

Probably variations in the pattern of distribution of

patent ductus arteriosus, are at times transmitted through successive generations. As a result of the large concentrations of congenital heart cases in places such as Paris (4), London (7) and Baltimore (6), excellent empiric risk figures are becoming available.

A second point: one is reminded of the work of Landauer and others (*Table 3*), *who can produce congenital malformations* with teratogenic agents with varying facility, depending on the genetic strain of the experimental animal. Ethyl carbamate produces cross-beak in 6.8 per cent of white leghorns and 25.4 per cent of black Minorca. Comparing two strains of mice, one with a 5 per cent sporadic incidence of cleft palate and harelip and another with a 0.2 per cent incidence, it is found (5) that cortisone produces a 100 per cent incidence in the 5 per cent sporadic group and only 18.7 per cent in the other. Genetic and intrauterine environmental factors may well collaborate in the production of congenital malformations of the cardiovascular system, as in other congenital malformations (2)—one is reminded immediately of Mongolism.

Atherosclerosis

The chart in Figure 1 is intended to indicate some of the factors responsible for atherosclerosis. I do not apologize one whit for its complexity, since this is the nature of the problem and this chart is doubtless already a gross oversimplification. Both environmental and genetic factors are multiple. The proportion of each varies from case to case. Stress may contribute to hypertension and possibly even to hypercholesterolemia, both of which accelerate atherosclerosis. Diet, by reason of excess fats or the wrong kind of fat, perhaps by reason of deficiencies of pyridoxine, and possibly by other mechanisms not now known, may contribute to atherosclerosis. The genetic predisposi-

diet of the general population, on the premise that such changes will definitely lessen the incidence of coronary or cerebral disease." However, the report does state: "These conclusions obviously apply to the general population, and not to patients or to individuals with a strong family history of early deaths from cardiovascular disease." One is reminded of the well-known story of the man accused of stealing a jug: "Why, I have never as much as seen that jug; furthermore, it was cracked anyway."

The young coronary artery patient has been the object of study by several groups, including Yater (13) who used an army population, and by Gertler, White, and others (3), who used a hospital and private practice population. Such studies demonstrate peculiarities that may have a genetic basis. For example, Gertler and colleagues (3) found a deficiency of ectomorphic individuals in the young coronary population.

For prognosis and prevention, we should have information on what the young coronary victim looks like as a child and teen-ager. For this reason, we have undertaken to focus on the children of young coronary patients as much as on the proband.

Hypertension

In essential hypertension we again encounter the problem of multifactorial causation, which is probably in part environmental, in part genetic. There is some reason to think that blood pressure is a continuous variable, which is age and sex dependent. The state we choose to designate hypertension is the arbitrary truncation of a distribution curve.

As in the case of atherosclerosis, in which the genetic factor is easiest to demonstrate in young coronary artery

arteries, such as the coronary and the cerebral, are to
some extent genetically determined. These variations may
be critical in determining the clinical effects of thrombosis
and possibly some varieties may predispose to atheroscle-
rosis through hemodynamic peculiarities. Accumulation
of data on intrafamilial similarities of coronary or cerebral
arterial patterns is difficult, requiring, as it does at present,
necropsy determination. Wilkinson (12) postulates that
atherosclerosis is "a process in which an inherited defect
of arterial structure permits the development of placques
under the influence of secondary factors, such as hyper-
tension, renal disease, and certain hormone imbalances."
He pictures this arterial abnormality as "an inherent defect
at the junction of the intima and media." This suggestion
should stimulate productive work. It *is* known that the
coronary arteries of the male have a greater intimal thick-
ness than those of the female from the early stages of
development. Some families have a genetic defect of lipid
metabolism, leading to hypercholesterolemia, in such pro-
nounced form that it is possible to analyze this factor
which overshadows the others. Reference is made to the
work of Adlersberg (1), Wilkinson (11), and others (10).
A genetic defect in the plasma-clearing mechanism is only
speculative. There are other factors that influence blood
lipids but are not covered in Figure 1, e.g., exercise and
hormones.

The family history is of utmost importance in *diagnosing*
coronary artery disease, let us say in a young man with
chest pain, and in the *planning* of a dietary or other pro-
gram for an individual or a family. In a recent joint report
(8) the statement was made: "The evidence at present does
not convey any specific implications for drastic dietary
changes, specifically in the quantity or type of fat in the

diet of the general population, on the premise that such changes will definitely lessen the incidence of coronary or cerebral disease." However, the report does state: "These conclusions obviously apply to the general population, and not to patients or to individuals with a strong family history of early deaths from cardiovascular disease." One is reminded of the well-known story of the man accused of stealing a jug: "Why, I have never as much as seen that jug, furthermore, it was cracked anyway."

The young coronary artery patient has been the object of study by several groups, including Yater (13) who used an army population, and by Gertler, White, and others (3), who used a hospital and private practice population. Such studies demonstrate peculiarities that may have a genetic basis. For example, Gertler and colleagues (3) found a deficiency of ectomorphic individuals in the young coronary population.

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As in the case of atherosclerosis, in which the genetic factor is easiest to demonstrate in young coronary artery

patients and in patients with a striking lipid defect overshadowing all other factors, so in hypertension the neatest category for study would appear to be malignant hypertension, that is, accelerated phase of essential hypertension. Some workers find a striking family history of hypertension in the majority of cases of malignant hypertension; when such a history is absent, primary renal disease or similar specific cause of the hypertension is suspected. (The results of some other workers are not in agreement, however.)

Pharmacology has two major divisions. One concerns itself with the question of whether a given drug is effective, the other with the mechanism of drug action. In clinical genetics we have a comparable dichotomy: Is there a genetic factor in a given disorder? What is the mechanism by which a genetic factor operates in the production of a given pathophenotype?

In our department Humphreys has recently demonstrated, by an ingenious method, the heritability of a tendency to hypertensive toxemia of pregnancy. He studied 100 toxemic women who were themselves born in the Johns Hopkins Hospital, and whose mothers, by reason of the latter fact, were observed at that hospital during at least one pregnancy. For the purposes of this study the hypertensive toxemia was defined in terms of blood pressure only, and diastolic blood pressure in excess of 90 was the criterion. Systolic blood pressure was not used because of apparent variability on exogenous bases. No one was included in the study who by any evidence was a chronic hypertensive on any other basis, such as pyelonephritis. Another aspect of the study was a follow-up on the mothers of these women, done exclusively through the unit records of the patients, so 60 or 65 per cent in each group had ten-year follow-ups, and approximately 5 per cent had

twenty-year follow-ups. When he compared this group with a similar group of 100 non-toxemic women, likewise born in the Johns Hopkins Hospital, Humphreys found an incidence of hypertensive toxemic over two and a half times greater in the mothers of toxemic daughters than in the mothers of normotensive daughters (Table 4).

TABLE 4. INCIDENCE OF HYPERTENSIVE TOXEMIC

	Number in group	*Experienced toxemia*	*Born of toxemic pregnancies*
Probands	100	100	28
Controls	100	0	11

Thus, a familial and very likely a genetic factor has been demonstrated, but what is its mechanism, how do the toxemic lines differ from the nontoxemic lines?

Another colleague of mine, Caroline Bedell Thomas (9) has proposed certain guideposts in the prevention of heart disease of the hypertensive and atherosclerotic types. These guideposts are derived from the experience of others and from her own in the study of Johns Hopkins medical students. Dr. Thomas grades the probability of developing cardiovascular disease in four classes, depending on the parental history for hypertension and coronary artery disease and on certain traits displayed by the individuals. These traits probably also have, in considerable degree, a genetic basis. Inexact and empiric as it is, this type of approach is one of the best we have for guiding preventive measures at the clinical level, that is, at the level of the individual. In effect, it is an attempt to place on a more concrete basis that vague quantity known as "clinical

judgment." A genetic assessment enables the susceptible individual to be pinpointed and prophylactic measures to be arrived at *more effectively*.

There is a prevalent conception that demonstration of a genetic factor means that treatment is hopeless. It is not necessary to point out to this group that such pessimism is unwarranted, that the ability to identify genetic susceptibles is the most promising attack on many of the major illnesses with which mankind is presently afflicted, and that solutions to these problems through preventive medicine will be closer when characterization of the genetic factor is complete.

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Introduction

BENTLEY GLASS

Recently at Stanford in an address that I was asked to give on the responsibilities of biologists, I made a rash statement to the effect that the biological discoveries of the next decade or so were likely to be as revolutionary in their impact on society as the developments of the atomic physicists during the past few decades. But I didn't go into *any analysis or discussion or description or* prophetic intonation to spell out what these revolutionary discoveries in biology that are just around the corner might be. The newspaper reporters, hopping on this and thinking that this would surely be news, were very much distressed that I wouldn't take on the role of a prophet.

Here, in a smaller company, where I hope no newspaper reporters are listening in, I might be somewhat more rash, because I think it is relevant to this topic of heredity counseling. I think we cannot look just at the situation as it exists at the present time and at the problems that confront those who want to give advice in respect to heredity to inquirers. We have also necessarily to look ten or twenty years ahead, if we can with reason do that, and begin thinking about the problems that are going to face heredity counseling then, and what responsibilities will rest upon those who take on this role.

I might suggest, for instance, that the impact of effective control over conception—the development of new steroid

that artificial control of sex determination is not too far around the corner. What kind of advice are we going to give when we are faced with problems in this area?

And there has been an even more startling announcement from biologists in France, who reported that, by inoculating into the eggs of young ducklings of one genetic strain of ducks an extract of deoxyribose nucleic acid from a different strain they were able to bring about a transformation of the genetic type. This has not been confirmed yet. Whether actual transformation of genes or of the effects of genes can be brought about in this way is not clear, but with recent developments and methods of artificially synthesizing the hereditary material of bacteria it seems certain that within a few years we will have a much better knowledge than we do now of the chemical structure of the hereditary material. And if a transduction is a phenomenon that you can find in higher animals as well as in bacteria, it seems possible that we might eventually be substituting desirable for undesirable genes in the germ cells of certain genotypes.

These are problems that I am sure we are not likely to want to discuss now. I just suggest that heredity counseling is, in the next few decades, going to steer into stormy waters. If we can give some thinking to these problems in advance and clear up questions of our own ethics in relation to such things, we may be better prepared when the time comes.

pills that can produce complete, temporary abeyance of menstruation—is one thing that is going to alter the picture very considerably in this and related fields of population problems. Not only is this harmless and effective contraceptive going to bring about a very radical change, but the techniques of artificial insemination that have been well developed by the cattle breeders offer possibilities again with respect to the human population that raise legal and ethical problems that the heredity counselor is also certain to become concerned with.

I often think that it may have been a good thing that Lysenko was in power in Soviet Russia during the days of Stalin, who had a certain desire to see his own offspring live after him. The possibilities of freezing semen and using artificial insemination after considerable periods of time raise possibilities that perhaps the science fiction writer has dealt with but that we might actually have to face up to.

And then, if there is any credence at all to be placed in the reports of artificial parthenogenesis in mammals—(I am not referring to the discussion that took place in the newspapers in Great Britain some time ago but rather to the experiments of Pincus and Chang with rabbits)—if parthenogenetic rabbits have been produced, then it would seem theoretically that there can be no reason why parthenogenesis could not be employed in the human species, too. This also raises questions that may lie ahead of us in the future.

In the Proceedings of the National Academy of Sciences a paper has been published on the separation by electrophoresis into male-determining and female-determining elements in the spermatozoa of the rabbit, not with complete efficiency but with sufficient efficiency that if the method can be applied to human semen it seems possible

takenly classed as unaffected. These diagnoses and examinations require the services of one or more physicians, who often must be assisted by clinical laboratories of various kinds.

The minimum professional staff of a heredity counseling service is, consequently, one human geneticist and one physician. Neither of these persons need necessarily work full time in providing counseling service, but they must be able to work together as a functioning team. The most favorable situation is where the heredity counselor is at the same time both a human geneticist and a doctor of medicine. Unfortunately, very few persons have this combined training. Usually, therefore, the geneticist must be a different person from the physician.

Not every geneticist with special training in human heredity nor every physician will make a successful genetic counselor. A broad sympathy with human frailties is needed as well as knowledge of the wide distribution of human defects. The counselor must be able to give due weight to all the hereditary features of each kindred that comes to him for advice. He must be able tactfully to call attention to the average and to the superior heredity the family carries as well as the particular defect that has brought the family to his attention.

In addition to the professional staff of geneticist and physician, a heredity clinic needs a secretary to copy and file records, answer correspondence, make appointments, and otherwise keep the work running smoothly. A laboratory assistant to draw pedigrees, make photographs, type bloods, and do other related types of laboratory work can be of great help. For certain kinds of study there may also be needed a field worker who can visit relatives in their homes and make appointments for certain of them to come

5 The Structure of Heredity Counseling Services

LEE R. DICE

When it is desired to organize a heredity counseling service the first question asked is: "What facilities are needed to organize such a service?" This is not an easy question to answer because local situations vary greatly. As a partial answer I submit the conclusions I have reached from my own experience in organizing a heredity clinic at the University of Michigan.

PERSONNEL

Personnel is the most important factor in any effective counseling service, so let us first consider the staff. At least one staff member of the service must, of course, be thoroughly versed in human genetics. This geneticist must be competent to analyze family pedigrees and to ascertain, so far as may be possible, the mode of heredity of the trait or traits in question in each particular kindred under consideration.

Many of the questions asked of a counseling service pertain to medical traits. Diagnoses of the affected members of each kindred must be obtained or verified. The presumed normal members must usually be examined also in order to be certain that no affected individual is mis-

versely, the hospital staff may easily refer their patients to the Heredity Clinic for advice about heredity.

FINANCIAL SUPPORT

Financial support for any heredity counseling service is difficult to secure. Few persons would be willing or able to undergo the considerable expense required to make the necessary examinations and diagnoses of their relatives before dependable advice about their heredity could be given. Those families most in need of genetic advice often are the very ones least able to pay for it. Furthermore, many of those individuals who greatly need counsel about their heredity are so little interested in the subject that they would refuse to pay any fee at all.

The Heredity Clinic of the University of Michigan is supported through the Medical School as a part of the training of medical students and to provide material for research in human genetics. Heredity counseling services elsewhere are supported in various other ways.

This problem of financial support for heredity counseling needs much careful consideration and experiment. Probably the problem will be solved differently by different communities.

Human heredity actually is a phase of public health. The heredity of the population should be of at least as much concern to each commonwealth as are infectious diseases. I look forward to the time when heredity counseling will be available in every large center of population. Such a development, however, is not likely to be achieved in the near future. For one thing, it would be impossible to staff more than a few such services with the geneticists

to the clinic for examination or for the physician to examine them in their homes, if this is possible.

A heredity counseling service need not always be organized as a special administrative unit. Counsel in heredity is being given by a number of human geneticists who are not associated with any organized counseling service. Co-operation with one or more physicians is nearly always required. A disadvantage of such an arrangement is that, lacking a formal organization, the service will probably be discontinued when either the geneticist or the co-operating physician is unable to continue. A handicap is that the geneticist may find difficulty in securing access to all the confidential medical information he may need to complete his pedigree analyses. Furthermore, such co-operative undertakings must usually be on a part-time basis for the staff members and one or more of them may find difficulty giving the work the attention it needs. For these reasons, I strongly recommend that every heredity counseling service be organized on a permanent basis with adequate staff to provide the needed service.

LOCATION

The most favorable location for a heredity counseling service is in association with a well-equipped hospital. The Heredity Clinic of the University of Michigan operates as a unit of the University Hospital and has the same position as any other of the hospital clinics. This favorable administrative location gives the staff of the clinic access to the hospital records, use of the clinical facilities of the hospital laboratories, and freedom to ask advice from any of the members of the hospital professional staff. Con-

versely, the hospital staff may easily refer their patients to the Heredity Clinic for advice about heredity.

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now available who have had training in genetic counseling.

Interest in genetic counseling, however, is rapidly spreading. Knowledge of the mode of heredity of human defects also is expanding. It is only a question of time, in my opinion, before heredity counseling service will be demanded by communities all over the nation.

6 The Meaning of Empiric Risk Figures for Disease or Defect

JAMES V. NEEL

In genetic counseling extensive recourse is had to "empiric risk figures" In general, such figures are statements, based on experience rather than an understanding of etiological mechanisms, of the likelihood that a particular condition will be present or develop in a particular individual under a particular set of circumstances. For example, we have empiric risk figures for the likelihood of the recurrence of a child with a harelip, once such a child has been born to parents normal in this respect, whose antecedents were likewise without the trait. Or, using the same trait as an example, we have empiric risk figures for the likelihood that when an individual with a harelip marries a normal individual, the children of this union may be expected to exhibit this trait.

Empiric risk figures are usually assembled as follows: an investigator interested in a particular trait, say harelip, takes a careful family history each time he examines an affected individual. Let us say that he finds that 100 such individuals, all born of normal parents, have 300 siblings, of whom 15 exhibit a harelip. The empiric risk of encountering this trait among the siblings of an affected

individual is thus 5 per cent, and this risk could then be applied to the probability of any future siblings of such an individual exhibiting the defect.

A question that often arises in the derivation of risk figures is whether all the siblings of an affected individual should enter into the derivation of the risk figures, or only those born subsequent to the affected propositus. Many of the empiric risk figures in the medical literature have made use of all siblings. In so doing, there is the tacit assumption that the risk remains constant with parental age and parity. With respect to congenital malformations, a class of defects for which empiric risk figures are commonly used, this is not a correct assumption, the frequency of congenital defect rising *significantly* among the children born to older mothers. Thus, in the Japanese material described by Dr. Schull and myself (5), congenital defects are two to three times as frequent among the children of mothers over 40 than the children of younger mothers; and this increase has not as yet been shown to be associated with any particular defect or group of defects. In the case of congenital defect, then, truly accurate empiric risk figures should probably be based only on children born subsequent to the birth of the first affected, although the actual correction so introduced will not usually be large.

In the case of Mongolism, one of the most frequently encountered congenital defects, this age effect is especially striking. Thus, among all the siblings of children with Mongolism, the frequency of Mongolism is about 1 per cent. However, among children born subsequent to the birth of a Mongol, the frequency of the condition is about 4 per cent. The latter is the correct empiric risk figure, since it is the subsequent children whom the parents are inquiring about (1).

An empiric risk figure carries no implications concerning etiology and is, in fact, an expression of ignorance concerning etiology. Where the genesis of a particular trait is understood, one need not rely on empiric risk figures. For instance, consider a very rare, recessively inherited syndrome. As material on this condition accumulates, it will first become apparent that there is an appreciable recurrence risk. It will also become apparent that there is more consanguineous marriage among the parents of affected individuals than in the population at large. In time, the recurrence risk will be shown to approximate 25 per cent and the data will justify the conclusion that this is a recessively inherited trait. At this point, one can base one's predictions on a specific genetic mechanism.

An important corollary of the fact that empiric risk figures reflect our ignorance as to precise etiology is the conclusion that the application of such figures to the individual case may in reality be quite misleading. Thus, current thought concerning the etiology of congenital defect clearly emphasizes the concept of multiple causative factors. Some individuals with such a trait as harelip may owe the condition to a transient disturbance of maternal metabolism during pregnancy or to a pure accident in the complex machinery of development, an accident that has no increased probability of repeating itself. Other such individuals may owe their condition primarily to their genetic constitution. Finally—and I suspect this is the largest group—the trait in some individuals may result from an interaction between features of the intrauterine environment and the individual's genetic constitution, i.e., the combination of "environmental" factors with a prepared soil. One over-all risk figure applied to all these cases will in some instances overestimate the risk, and in other

instances underestimate it. One of the really pressing needs in genetic counseling is the development of methods that will permit us to distinguish between these possibilities. Considerable progress has been made toward detecting *individuals who are the genetic carriers of various inherited* traits (reviews in 3, 4, 2). An extension of this same approach to the field of congenital defect may be fruitful, in that some parents might be found to exhibit on close scrutiny subclinical findings that would indicate they were the carriers of certain genes responsible for hereditary defect, while other individuals would not exhibit these findings.

The empiric risk figure employed in a genetic counseling problem is at best a tentative figure, subject to revision in the light of future experience. Thus, we have on several occasions been consulted by parents whose first-born has exhibited a very rare constellation of congenital abnormalities. Since empiric risk figures on this specific constellation were lacking, we fell back on the rule of thumb that there is in the neighborhood of a 3 to 5 per cent recurrence risk for most of the carefully studied congenital defects. This general figure, together with other pertinent information, was given the parents as a guide *for their thinking. However, it was always emphasized* that simple recessive inheritance could not be ruled out, and if they should have the misfortune to have a second child with the same combination of defects, then a revision of the recurrence risk may be in order.

Finally, to round out this presentation, I should state the obvious, that empiric risk figures are no substitute for a careful family history. Such a history will sometimes delineate high risk families, to whom the ordinary figures do not apply.

In summary, then, empiric risk figures are essentially pragmatic probability statements based on accumulated medical statistics. The figure employed for any specific defect undoubtedly encompasses a number of different etiologies. A task confronting human genetics is to learn to distinguish between these etiologies, a development that will put genetic counseling on a sounder basis.

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many counseling problems directly, and who will refer the more difficult problems to the specialist in genetics.

Establishing contact with patients needed for research projects can be done in a variety of ways. Usually a method is required for obtaining an unselected and statistically unbiased series of patients of a type suitable for the research plan. Often this will depend on the establishment of close rapport between the geneticist and the house staff of the teaching hospital. Arrangements should be made with the chief of the proper service for notification on admission of any patient suspected of having the condition selected for study. This should be supplemented by an arrangement with the record librarian to obtain notification concerning all hospital records received bearing the desired diagnosis as these records are received on discharge of the patients. A plan of this type must be implemented by seeing the patients promptly and obtaining the necessary studies, and leaving a consultant's note on the hospital record, and also by conferences with the house officers concerned.

Research problems may also require the collection of information on a series of cases previously seen in one or more hospitals or clinics. As the patients are no longer immediately available, this requires a record search and usually home visits. The technique of conducting survey studies of this type was discussed extensively at the conference on problems and methods in human genetics held at the National Institutes of Health in October of 1953 and published in the *American Journal of Human Genetics* (3, 1, 2). In these studies contact with the patient is usually established by a field worker, and this contact is often made much easier by working through the family physician.

7 Procedures for Referral to Heredity Counselors

C. NASH HERNDON

The term "referral" should be interpreted broadly to include all mechanisms whereby the heredity counselor and the patient, or members of his family, come into contact. It may be useful to consider referral procedures in relation to the primary functions of a medical center. Generally speaking, a medical center has three major functions. These are, *first, teaching; second, research; third, patient care.* Many medical educators rank these functions in importance in the order given.

A teaching service requires a well-balanced variety of problems to provide a flow of suitable material for the purpose of training students and house officers. Most of the material needed for teaching can be provided by the *normal flow of patients found on any active pediatric and* medical service. This material can be readily utilized by making arrangements for the heredity counselor to attend ward rounds and staff conferences normally held on these services. Conferences with the students and house officers assigned to patients of genetic interest can be used to guide the student in collecting suitable pedigree material and in outlining *suitable advice to the patient or his family. This* function is particularly valuable in increasing the number of physicians in the community who are able to handle

standing between the counselor and the agency concerning the method of referral and the information to be collected and supplied by the agency. This can be made more effective if the counselor will give occasional educational and informational talks to staff meetings of agency workers and to other meetings of social workers, public health nurses, and other personnel concerned. In dealing with agencies, the problem of privileged communication must be handled with care. The counselor may submit a report to the agency only if he has written permission from the patient or his family to do so. The counselor must be careful to observe the pattern of medical ethics and the legal requirements for transmission of information to non-medical personnel. The patient will usually regard the counselor as equivalent to a physician in terms of doctor-patient relationships, and the counselor must avoid any action that could possibly be construed as malpractice. In this connection it is most important to keep an exact record of the advice given to the patient verbally and to keep records of all correspondence Even with agency-referred patients, it seems advisable to work with the patient's family physician if this is at all possible or to suggest that he obtain a physician

In addition to patients referred by others, some patients will refer themselves. The existence of a heredity clinic is often publicized in newspaper or magazine articles, and numerous mail inquiries are often received after such publicity. All letters so received should be answered, but much caution and tact are required. Some of these will be requests for general information, for example, students writing term papers, and these may usually be handled by a routine letter or by sending appropriate pamphlets. Requests for information on specific diseases or specific family

The function of patient care involves all referrals that are initiated by the patient, his physician, or a social agency, and will be unrelated to the research activities of the department. These referrals may be received in several ways. The staff geneticist may receive consultation requests on patients in the hospital or clinic from the attending physician in the usual consulting routine of the hospital. If the geneticist succeeds in demonstrating to his clinical colleagues his usefulness in the management of clinical problems, this consultation service can be expected to become rather heavy. Similar referrals may also be received from practicing physicians whose offices are located outside of the medical center. These referrals are usually made by letter or by telephone. The magnitude of this service depends upon the degree of genetic education of the physicians practicing in the community or area and their awareness of the usefulness and availability of the consulting service. In our experience the bulk of referrals of this type are received from physicians who took courses in medical genetics as students or were house officers in a teaching hospital with a genetics service. Awareness of the usefulness of this service can be stimulated by talks to county medical societies and other medical groups. It is important to maintain an efficient appointment schedule and to report findings and recommendations by letter promptly to the referring physician. The patient should be encouraged to remain under the care of the referring physician, and the consultant should work in co-operation with the referring physician.

Referrals may also be received from various social agencies, including welfare departments, health departments, adoption agencies, and various private service organizations. These must be based on a mutual under-

standing between the counselor and the agency concerning the method of referral and the information to be collected and supplied by the agency. This can be made more effective if the counselor will give occasional educational and informational talks to staff meetings of agency workers and to other meetings of social workers, public health nurses, and other personnel concerned. In dealing with agencies, the problem of privileged communication must be handled with care. The counselor may submit a report to the agency only if he has written permission from the patient or his family to do so. The counselor must be careful to observe the pattern of medical ethics and the legal requirements for transmission of information to nonmedical personnel. The patient will usually regard the counselor as equivalent to a physician in terms of doctor-patient relationships, and the counselor must avoid any action that could possibly be construed as malpractice. In this connection it is most important to keep an exact record of the advice given to the patient verbally and to keep records of all correspondence. Even with agency-referred patients, it seems advisable to work with the patient's family physician if this is at all possible or to suggest that he obtain a physician.

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problems are potentially dangerous and must be handled with care. In our experience information given in such letters is often erroneous and could lead to improper advice if one attempted to supply genetic counsel upon such inadequate information. It is surprising how often such letters give incorrect diagnostic information, apparently resulting from misunderstanding or misinterpretation of verbal information received from physicians. Giving genetic advice on the basis of an unsupported letter should be avoided. Every effort should be made to induce the patient to consult his family physician and obtain referral through this source, or to have the patient visit the clinic for both diagnostic examination and genetic study. It is often possible to give suitable advice to a physician for transmission to a patient that cannot be seen in person, but this should be based only upon accurate diagnostic and pedigree information collected by the referring physician.

A final type of referral is that which may be received from a court in medicolegal cases. These must also be handled with care to meet the legal requirements for blood group testing. Arrangements for blood testing are usually made by attorneys and upon court order. Care must be taken to maintain the legally required chain of evidence. The individuals concerned must be properly identified, and preferably the opposing parties to the action should identify each other in the presence of the geneticist. Reports with proper interpretation should be sent direct to the clerk of the court concerned, with copies going to the attorneys representing both parties.

In summary, patients may be referred to the genetic counselor in many ways and for many purposes. In general, it is advisable to work with the patient's physician if this

is at all possible. Due care must be taken to avoid errors that can occur as a result of incomplete diagnostic or inaccurate pedigree information, and careful record keeping and reporting to the proper physician or agency is essential.

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8 Types of Problems Presented to Genetic Counselors

F. CLARKE FRASER

My discussion will be limited to what kinds of questions genetic counselors are required to answer, how many cases they may expect to deal with, and where the questions come from. In order to get some information to talk about, I sent a rather rough-and-ready questionnaire to some of my counseling friends, who have been very generous in their response, and whom I would like to thank for their co-operation. The object was simply to get some impressions of the sort of case-load carried by counseling centers, and no claims to statistical validity are made. The questions dealt with the number of cases referred per month, what proportion were referred from hospital wards, practitioners, or came directly, what categories of questions were asked, and the five most frequent conditions encountered.

NUMBER OF CASES

The first question dealt with the number of cases per month referred for genetic counseling. The answers would depend somewhat on the method of classification; some correspondents might include referrals for zygosity diagnosis in twins, for instance, and others might not. The

answers ranged from 1 to 40 referrals per month. This volume might be expected to rise somewhat as the benefits of genetic counseling become more widely appreciated. However, it seems unlikely that counseling centers will ever become self-supporting on the basis of income from fees. (This is one of the problems of genetic counselors.) No information concerning fees was gathered by the questionnaire, but it seems from personal conversation that at present fees are usually not charged.

SOURCES OF REFERRALS

The sources of referrals would be expected to vary widely according to the organization of the particular center, and so they did. Counselors associated with medical centers received anywhere from 20 to 80 per cent of their referrals from the hospital wards. The proportion of cases referred from physicians varied from 10 to 80 per cent, and the proportion that came directly to the counselor varied from 0 to 90 per cent. Some centers actively discourage the direct approach, and one center insists that referrals shall be through a practitioner or hospital. Our department does not employ such a hard-and-fast rule, but we believe that in genetic counseling, as with any medical specialty, the practice of referring cases through medical sources should be encouraged. For one thing, it is easier to get reliable medical information about cases referred in this way, and, for another, the counselor is given added prestige in the eyes of the patient by this approach. Additional sources of referrals are institutions and agencies, but referrals from these sources appear to be in the minority. Several centers, including ours, try to avoid giving advice by mail, although sometimes the person requesting

information is so remotely situated that there seems to be no alternative. I think several of you have had experience recently with a request from New Zealand for advice as to a contemplated cousin marriage. This person apparently also conducted a survey of genetic counselors—it would be interesting to see how much variety there was in the replies.

TYPES OF QUESTIONS

The questions asked of the counselor could be grouped in a number of categories. The most frequent type of question seems to deal with whether parents should have a baby, the problem arising either because they had already had a child with some disease of presumed or actual familial tendency, or because some such disease was present in one of the parents themselves or in some more distant relative. The next most frequent type of question deals with the desirability of a contemplated marriage, either because of consanguinity or some genetic disease in one of the families involved. Some cases are referred for an opinion as to the genetic suitability of an adoption procedure, some for an interpretation of the cause of a child's illness or defect (apart from eugenic considerations), some for an opinion as to the chances of a sibling or other relative of an affected person becoming affected in the future, and a few for other reasons such as paternity disputes, zygosity diagnosis in twins, dermatoglyphic diagnosis of Mongolism, and diagnosis of rare, obscure diseases. We have had, as yet, no experience with artificial insemination, although the procedure has been discussed in a few cases, and we have, as yet, had no requests for DNA transformations, although we are expecting one any day!

We did have quite a number of requests to diagnose sex before birth after the Richardson saliva test became known, and I might mention, incidentally, that although one could make the diagnosis with better than 90 per cent accuracy, a few cases that were wrong were so upsetting to the parents that they far outweighed the minor benefits of the ones that were right, and we no longer provide this service.

The specific conditions involved were of such great variety that there is little point in discussing them in detail. "Congenital malformation" was the group most frequently mentioned in the questionnaire. Others that appeared several times were neuropsychiatric conditions, consanguinity, Negro-white skin color, Mongolism, and Rh trouble. The type of condition referred would be expected to depend somewhat on the interests and situation of the counselor. Dr. Kallmann would no doubt find a high proportion of his referrals were neuropsychiatric problems, and Dr. Walker almost certainly gets a lot of Mongoloid imbeciles referred to her. Hemorrhagic diatheses form a large portion of the cases referred to Dr. Herndon, because of his hematological colleagues' interest in clotting mechanisms. Unlike some centers, we are hardly ever bothered with skin color problems, and the hematologist handles cases of Rh disease and disputed paternity. Most of the counselors questioned reported a "miscellaneous" category including a wide variety of rare but relatively clear-cut diseases, too numerous to mention here, and it would seem probable that a large part of counseling practice deals with cases of this sort.

I shall be interested to hear how well, or badly, these rough impressions of the nature of a counselor's practice correspond with those of other members of this group.

9 Types of Advice Given by Heredity Counselors: I

FRANZ J. KALLMANN

The decision to save the least conformable topic of this interesting symposium for the very last, like fireworks, was an act of prudence rather than a reflection of hidden sentiments. With the types of advice given in heredity clinics depending primarily on the functional character of the clinic, the nature of the problems presented, and the professional qualifications of the counselors available, there can be no uniformity in this area. It is also clear that, while the unfolding of some inevitable differences of opinion may be both sparkling and noisy, the general effect of such fireworks is harmless and good fun.

In other words, even if I do not always see eye to eye with everyone on some psychiatric issues, we are still dedicated to a common cause. More specifically, we are all agreed that heredity counseling is an important and rather exacting task which requires a high degree of proficiency and must be learned. In the last analysis, the type of advice given can never be better than the level of professional competence of the counselor who is giving it. It is therefore doubly regrettable, as has been stressed by Herndon (3) and others (6, 8, 14), that although counseling in medical genetics is part of a preventive public health scheme, our training programs have yet to prepare future

heredity counselors for activity in this vital sector of public health work.

Under these circumstances, the simplest way of defining the kind of advice given by a heredity counselor would be to paraphrase Calvin Coolidge's account of a sermon on sin. Just as Coolidge's preacher was *agin it,* so we might say that genetic counseling should be *free of it*—at least as much as possible.

COUNSELING WITHOUT SIN

While there are major and minor sins in operating a unit for providing advice in matters of human heredity, this distinction may vary according to whether a counselor's concern is with premarital, marital, preparenthood or preadoption problems. If the contact is directly with the persons seeking counsel, rather than with their regular physician or a public health agency, the least pardonable sins in counseling work are violations of one of the following rules:

1. The responsibility of counseling should be delegated only to personnel who are professionally competent, tactful, and mature enough to empathize with persons in need of guidance. Such workers will always be mindful of the fact that as members of a health service team, they are expected to understand the age-old medical principle of *nil nocere.* Persons in whom fears of a crippling or fatal disease have been instilled or aggravated by thoughtless or strenuously realistic remarks of an inexperienced counselor are likely to misinterpret even the most logical kind of advice and may become as distressed and debilitated as if they were actually afflicted with the disease they dread (2, 7, 15). It makes little difference whether one has cancer or is mortally afraid of it.

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Under these circumstances, the simplest way of defining the kind of advice given by a heredity counselor would be to paraphrase Calvin Coolidge's account of a sermon on sin. Just as Coolidge's preacher was *agin it*, so we might say that genetic counseling should be *free of it*—at least as much as possible.

COUNSELING WITHOUT SIN

While there are major and minor sins in operating a unit for providing advice in matters of human heredity, this distinction may vary according to whether a counselor's concern is with premarital, marital, preparenthood or preadoption problems. If the contact is directly with the persons seeking counsel, rather than with their regular physician or a public health agency, the least pardonable sins in counseling work are violations of one of the following rules:

1. The responsibility of counseling should be delegated only to personnel who are professionally competent, tactful, and mature enough to empathize with persons in need of guidance. Such workers will always be mindful of the fact that as members of a health service team, they are expected to understand the age-old medical principle of *nil nocere* Persons in whom fears of a crippling or fatal disease have been instilled or aggravated by thoughtless or strenuously realistic remarks of an inexperienced counselor are likely to misinterpret even the most logical kind of advice and may become as distressed and debilitated as if they were actually afflicted with the disease they dread (2, 7, 15). It makes little difference whether one has cancer or is mortally afraid of it.

9 Types of Advice Given by Heredity Counselors: I

FRANZ J. KALLMANN

The decision to save the least conformable topic of this interesting symposium for the very last, like fireworks, was an act of prudence rather than a reflection of hidden sentiments. With the types of advice given in heredity clinics depending primarily on the functional character of the clinic, the nature of the problems presented, and the professional qualifications of the counselors available, there can be no uniformity in this area. It is also clear that, while the unfolding of some inevitable differences of opinion may be both sparkling and noisy, the general effect of such fireworks is harmless and good fun.

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2. Inasmuch as specific counseling problems of clinical genetics require evaluation in terms of the total health and adjustment levels of a given family, they should never be dealt with in an *impersonal* way. Mail order methods may be profitable in other fields of endeavor but not in counseling work. By correspondence it is difficult to form an opinion regarding the predictable stability of the home a young woman will share with her future husband after a psychotic episode, or into which a child with a calculable morbidity risk will be born.

3. If the genetic counseling problem presented concerns a clearly pathological trait, it is essential to bear in mind that the potential health risks connected with marriage on the one hand, and with parenthood, on the other, may differ so considerably as to call for opposite decisions and entirely different supportive reorientation designs (4, 5, 6). Whatever the preferential pattern of conduct with respect to the two issues may be, they are to be *kept apart* in most areas of genetic guidance and should not be subject to biased value judgments on the part of the counselor.

4. Persons requesting genetic advice cannot always be presumed to be capable of making a realistic decision as to the choice of a mate, or the advisability of parenthood, without support in the form of directive guidance and encouragement. As is true in recommending any restrictive regimen, persons coming to heredity clinics may have to be told *how* to adjust, for instance, to a childless marriage or a family deliberately limited in size.

It is undeniable that reality enforcement without guidance may create anxiety, conflict, and ill health (2, 7, 10) and, therefore, is inconsistent with accepted standards of medical ethics as applied to the work of related service professions in the field of public health (14, 15). Hence it

would seem inappropriate to withhold tension-relieving support from indecisive and perplexed individuals when it lies within our power to provide such help in a genetic counseling situation. It is possible, of course, that counseling problems of this kind are particularly common in a genetics department connected with a psychiatric institute. It is safe to assume, however, that similar problems are encountered in heredity clinics specializing in other areas of clinical genetics.

In line with the four rules for *counseling without sin*, every heredity counselor should be able to determine when he cannot refrain from giving "directions as to what clients should do" or when he cannot rely on the diagnosis presented to him (11, 12, 13). Even in those centers where genetic counseling is merely regarded as "a type of social work carried out by the geneticist or family physician" (13), its main objectives will not always be confined to promoting the happiness of married couples. Apart from creating "subspecialty barriers" within an important discipline that has much need of teamwork and co-operation (2, 15), such constrictive formulations may cause us to lose sight of the over-all mission of medical genetics in the field of public health.

Parenthetically, I think we should distinguish between plans for a genetic information center and those for a genetic counseling center. If someone from Arizona writes and wants to find out what is known about the genetic aspects of Tay-Sachs disease or some other disease, and if the given information is supplied by letter, I have not done any counseling. I have provided information.

My concept of genetic counseling refers to requests for guidance in the presence of familial disease, and this kind of activity should, in my opinion, not be handled in an im-

personal way. We have to know the people, their personalities, and their family situations before we give counsel.

Nor do I think that genetic counseling is always a one-shot proposition. It may not be possible to give all the required guidance in one session. We have no difficulty in getting people back after six months or a year.

One other point: Medical genetics is to me as important a specialty as radiology or psychoanalysis or any other professional service. It requires a highly specialized kind of knowledge and experience. The majority of general practitioners cannot be expected to have the degree of specialized training necessary for counseling purposes. They should know where they can get competent advice as to the genetic aspects of a family's problems. I think there should be departments of medical genetics, preferably in every state or in several areas of a large state. The public, the public health agencies, other medical specialists, and the general practitioners should know where they can get specialized advice in regard to genetic problems. Often I offer advice as to inheritance problems in the frame of our departmental activities; I do not render it as a practicing psychiatrist.

To illustrate the willingness of guidance-seeking people to co-operate with a *personalized counseling program*, I should like to quote from a rather typical exchange of correspondence. A few weeks ago, we received an airmail letter from a young woman in Georgia, which read in part: "I am engaged to marry a young man who has a history of abnormality in his family. His parents are alcoholics, and of his four brothers and sisters three are feeble-minded and unable to care for themselves. . . . I would like to have children after we are married, but would rather adopt them than have any ourselves if they were likely to be as

unfortunate as his brothers and sisters. . . . Would you please let me know what your opinion is in the near future, as we are planning to be married soon and this problem is causing us a great deal of concern. . . ."

Following our usual procedure, we advised the young lady that her problem was too important to be dealt with by mail. Among other things, it was suggested that she and her fiancé come to see us. Her reply speaks for itself: ". . . We have decided to take your advice and postpone any decision as to whether or not to have children until we can consult with you. Circumstances prevent our being able to come to New York at this time, but we are hopeful that by the first of the year it may be possible. We will contact you again at that time. Thank you for your courtesy" —a closing sentiment that echoes my own at this moment.

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10 Types of Advice Given by Heredity Counselors: II

SHELDON C. REED

During the past ten years Dr. Ray C. Anderson, Elving Anderson, and I have recorded 1,778 counseling cases as of July 1, 1957. This number comes from the daily log which we keep and which affords a starting point for follow-up contacts to determine the results, if any, of the counseling. Such contacts have been made sporadically in the past. It would be valuable to make a careful, systematic study of the first 1,000 cases as they are now old enough to permit a correlation of the clients' statements with their reproductive behavior subsequent to the counseling.

This record of counseling represents a great many hours given freely to strangers for which you expect nothing in return except your own satisfaction that you have done your best to help them solve their problems.

It would be very gratifying if these cases had all been correctly handled and the counseling carried out under ideal conditions. Obviously, such could not have been the case, nor do I know of any center where genetic counseling is entirely satisfactory The reasons for the less than perfect counseling techniques are many and are responsible for the less than perfect performances in any area involving personal relationships and social work.

The large number of counseling cases mentioned above

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couple will resent the statement and look elsewhere for a less dogmatic presentation of the situation. Conversely, if you again rest upon authority and tell the couple that there is no danger of a repetition of an abnormality, they may doubt the statement with resulting frustration. It would seem clear from the whole of our cultural experience that people do not wish to be *told* how many children they can have. This is the reason that most genetic counselors emphasize that decisions regarding reproduction must be made by the couples themselves. Furthermore, I can assure you from both my personal and professional experience that the couple is not prepared to make their decision about subsequent reproductive intentions at the time they get the genetic counseling. They *will* take their time and think over what they have learned, or thought they learned.

There is a fundamental difference between psychiatric and genetic counseling. The psychiatrist can expect and demand a number of sessions with the patient. The genetic counselor cannot demand this and usually expects to have only one meeting with the clients. If there are two or even three meetings with the couple, it often means that a poor job of teaching was done at the first meeting. Genetic counseling is a one-shot proposition, most of the time. Subsequent to the birth of a child a couple may reappear for a further evaluation of the situation.

The experience at the Dight Institute is the same as what seems to have occurred in Denmark at Professor Kemp's Institute of Human Genetics. The proportion of personal contacts with the people involved is diminishing. The proportion of phone and mail contacts with the client's physician is increasing. Phone and mail contacts are not satisfactory methods of counseling and, knowing this, some

represents a general genetic counseling practice that could be expected to come to any person identified as being experienced in human genetics. Generally, the clients do not expect nor want very much beyond the genetic information, *and an understanding of it*, for which they have been referred by their physician, frequently an obstetrician. Of course it would be highly desirable if the counselor could have had several years of practice in obstetrics, pediatrics, psychiatry and hematology, to name a few of the pertinent disciplines, in order to gain a solid background in all fields. Probably the best that can be hoped for, however, is that he might have an M.D., in addition to his Ph.D. in genetics. These fields are all important in counseling, and there are many other ones that would be equally useful, such as legal training and social work. I assure you that training in all these disciplines and others would be most helpful in answering the questions posed in general genetic counseling. As no one could ever qualify as an expert in all these areas, genetic counseling will always be somewhat imperfect. Furthermore, if a person did qualify in all the most important areas, he would have reached a pinnacle of professionalism that would make him the world's worst genetic counselor. Professionalism leads to a kind of aloofness and austerity that expects automatic acceptance of the pronouncements given. As these expectations may exceed actualities, bitterness may result and the counseling has failed. As the old gag goes, "You can always tell a Harvard man but you can't tell him much."

What you can tell a person or couple depends upon the situation, which is practically always unique. If you say to the couple, as many physicians have said, "You must not have any more children," there is a good chance that the

attitudes are established early in life and modified only over a long period of time. If the genetic counselor attempts to sell any particular reproductive attitude too vigorously, he will certainly be rebuffed. Even the obstetrician cannot extensively explore his patient's mind on the subject of reproductive attitudes at the first meeting.

When the day comes that we have information about the heterozygote, how are we going to answer certain questions? We know that in neurological disease the age of incidence is rather young, so that a person with a dominant gene, unless killed in an accident, may live to face a 50 per cent risk that he will develop the disease. The day is probably coming when we will be able to predict that a certain individual will have this disease, that three sisters are not going to have it, that one of their brothers perhaps is. Can we benefit those who are not going to have the disease by telling them they are not? And refuse to say anything to the one who is going to have it? I have been exploring this for a long time with our Department of Psychiatry; unfortunately, it has not been helpful. I suspect that this problem must be faced before long.

In conclusion, it should be clear that to me the people who come for genetic counseling are clients and not patients. They are just as normal as the clients of a lawyer or social worker, or perhaps more so because, in general, they are fairly literate, or they would not know about you or seek advice from you. They come for information that they hope will relieve their anxieties about the future. Fortunately, the information obtained almost always does seem to diminish their fears and stabilize their thinking. They very frequently ask: Is there a chance that I can have any normal children? The chances may be 97 per cent that the next child will be normal, using risk figures for some

of the physicians refer the couple to the counseling center, but some do not. It is clear that the main body of counseling in medical genetics in the future will be done by physicians not located at counseling centers. This should be obvious. There are many thousands of families who have questions about human genetics. They are not located anywhere near a counseling center and have never heard that such exist, and, naturally, they ask their family physician whatever question they have in mind. The eventual remedy, of course, for the difficulty here is better training for the physician in human genetics so that he can do adequately the bulk of the genetic counseling, which is coming to him already, and which in many cases he does not do adequately now.

The question is still before us as to what to tell the couples that do come to the Dight Institute for counseling. While we cannot order them to produce a particular number of children related to the gravity of their situation, we can guide them to some approximate understanding of what the risk actually is. This is a tough job in itself, as the clients do not usually have much comprehension of probability even in the simplest penny-tossing form. If the risk picture can be satisfactorily transmitted to the clients, they will eventually try to fit their reproductive behavior to it. The means by which they do this will be influenced by the cultural and religious pattern in which they were reared. It is not likely that the genetic counselor can change these attitudes very greatly with the one shot he has. Furthermore, the clients in general know about the techniques, and only once in my experience has any client thought that I could personally fix her up with the changes that she wanted to take place. Most of them realize that this function obviously belongs to somebody else. Reproductive

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11 Discussions: Heredity Counseling

PROBLEMS OF THE GENETIC COUNSELOR

CLARENCE P. OLIVER

In most of the papers here there is very little that is controversial, they have done the job so well that I rather hesitate to make many comments. But I do want to be certain that some things have not been misunderstood, or will not be misunderstood, and I want to bring out one other point that has not been covered.

Dice's paper suggested that there be accurate diagnoses, including the diagnosis of normalcy for those who are reported to be normal Actually, in studying human genetics, accuracy is extremely important. You will find, if you are working with a characteristic not present very early in life, that the proband will probably know more about her mother than about her sister, and certainly more about her sister than about some distant relative. It is also true that she will know more about her father than about her brother. You do find occasionally individuals who are classified as normal, not only by the proband with whom you begin your study, but also by other relatives. And yet when you go to the individual to verify or confirm this normalcy, you find that the individual is not normal.

I know one case of breast cancer in which a woman had

of these common indeterminate risks that Dr. Neel has mentioned. The presentation of genetic information is the primary function of the genetic counselor. The presentation must be compassionate, clear, relaxed, and without a sales pitch. You will know whether you have succeeded or not as a result of the completely voluntary messages that come in from the clients some years after the counseling. You learn that in many cases, at least, your efforts were not in vain.

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letters will not ordinarily give us sufficient information about the trait involved. You want to get accurate information when you can, but when you cannot, you still may want to—and you should—give a tactful answer to the person who writes the letters.

I believe that should be done, because I feel that most of those who write in for information have a problem disturbing them. As one human being to another, if for no other reason, you should do the best you can to relieve their anguish or to tell them exactly what is known about the possibility of this trait developing.

Sometimes a person who writes to a counselor lives all the way across the country from the counselor. The letter is sent for a particular reason, and I think an example will be the best way for me to explain it to you.

One individual first wrote a letter and then, eventually, came in to talk about his problem. After the discussion he was asked why he did not to go to a geneticist living close to him, although not in the same city, to get his information. His answer was that if the people in his home area found out about the complication he was involved in, he would be socially ostracized and economically ruined. Therefore, he did not dare go to someone who could answer his question but who also lived close by, because there was a possibility that the news would leak out. So he spent considerable money to talk to someone at a distance.

I want to mention something about finances, too. I certainly am not going to plead for charging of fees. I do not believe in it It is perfectly justifiable if you are a physician examining the individual for medical data; but in so far as genetic counseling is concerned, I do not believe in charging fees. I would not want to attack anybody else having a different belief, however.

This position was questioned once by someone who

had both breasts removed—mastectomy—and none o
sisters, none of her nieces, knew anything about this a
She had kept it quiet from everyone, but she did give
information to us, and we were able to confirm this
going to the hospital records.

I would like to make a statement as well about a point
Neel's paper that does not differ from his, but is somethi
I wish to emphasize. It involves the impossibility of reco
nizing individuals who have a particular genotype an
who thereby carry the potentiality to develop a particula
phenotype in time.

It would seem obvious to most persons who have worked with experimental genetics that you can get a mimic of a hereditary condition, the mimic resulting from some environmental factor, and the mimic will not necessarily be identical with the hereditary type. But the fact that you have some slight variation is not in itself evidence that you are dealing with something nonhereditary. Even when you induce mutations, that is, gene changes as we describe them, you will not necessarily get the same phenotype in the second mutation that you got in the first mutation. You may describe them as exactly the same, because your eye is accustomed to seeing some visible variant, and it is the first characteristic you recognize.

Often you will find some new variation intermediate with respect to two hereditary traits, both recessively inherited, and both involving primarily a particular part of the body. This variability of traits is something that we need to find out more about in human genetics, if we want to make good use of family histories in working out the data for use in counseling.

I believe that the authors of these papers recognize the need of following up, or at least answering, letters that come to them, even though all of us recognize that these

the outside for that purpose. There are possible sources for those funds, but at present there would not be a large amount available for any one group.

CONSIDERATION OF THE WHOLE PERSON

HAROLD F. FALLS

American medicine has experienced cycles of specific interest and now, after a rather long preoccupation with mechanical gadgets and instrumentation, has again turned to a consideration of *the individual as a whole person.* The physician in such a consideration must necessarily investigate the patient's economic status, social responsibilities, social attributes, level of education, reaction of the psyche to the illness and particularly the hereditary make-up. The patient and his disease must, therefore, be carefully evaluated in the light of the combined influence of that individual's environment and hereditary make-up. The human geneticist and/or counselor, perhaps better than any other discipline, needs to employ this careful consideration of the individual *as a whole person.* In order to give a satisfactory genetic prognosis, the counselor requires the following aids: (1) careful and accurate diagnosis, (2) meticulous study of the specific individual's family and (3) a thorough knowledge of the medical and hereditary literature dealing with the specific trait or traits being studied. It is not always possible to fulfill these requisites necessary to the giving of a genetic prognosis. The counselor, therefore, should possess that most important attribute, honesty. The limitations of available knowledge and difficulties of accurate diagnosis should be admitted freely and demonstrated to the inquiring individual. Recent at-

said that I preferred to be a gentleman rather than a worker, and that may be it. I don't know. Actually, I just feel that most of those who come to us for information are not able to pay fees, and that if we in genetic counseling begin to charge fees many will look upon us more as professional individuals and not as human beings. I apologize to anyone who may think I am saying he is not human because he is professional. I hope you will see what I mean; that it is essential that you treat these individuals as fellow men who have problems, for they want someone to whom they can turn in confidence to discuss problems and to get some honest advice about the possibilities, even though you cannot keep them from developing the trait because medical knowledge has not progressed that far.

There has been little said about training. It is doubtful that anyone could set up a program for training in genetic counseling. Some individuals might conceivably be able to do it, but most of us could not. It certainly is true that not everyone could be trained to become a genetic counselor. There are excellent geneticists who could not learn to act as counselors even though they know all the subject matter in human genetics. There are physicians, of course, who are accustomed to counseling, but they may lack sufficient knowledge of genetics, and many of them would not go into genetic counseling. Possibly some of those could be trained to become genetic counselors. You do need some means to train individuals in genetics, if they do not know the field, and to give them a broader knowledge in human genetics if they already know basic genetics.

That can be done only if certain schools where individuals who can give this training are located will develop a program of training in human genetics. That means as well that the school ordinarily will have to get funds from

textbook picture in each of a hundred cases of measles but rather anticipate differences in the manifestations and the course of the disease. The geneticist must educate the physician to realize that no one gene acts alone but rather experiences a very complex interaction in the gene milieux of the affected individual. Since this gene composition varies greatly in every individual (except monozygous twins), significant variations in both expressivity and penetrance of the gene should be expected. The textbook picture expression of a gene effect therefore is seldom observed; rather variation becomes the rule. These differences in expression of many disease traits are perhaps further accentuated or brought about by differences in the environment of the affected individuals.

The most important requisite of any genetic counselor is the possession of a high degree of common sense or, to put it more bluntly, just plain "horse-sense." The effect of any specific trait on an individual's ability to become a useful member of society must be weighed carefully in giving genetic advice and in addition upon the mental status and social standing of that individual's family. The singular fact that such prospective parents actually seek genetic prognostication indicates a greater degree of intelligence and social and moral responsibility on their part than is true of a large proportion of our population. Such parents, perhaps, should actually be encouraged to have children (anticipating transmission of superior qualities) providing the gene to be transmitted does not impose too serious a handicap on the affected child.

In respect to lethal traits (Tay-Sachs disease, for example) the counselor, if convinced that the parents possess better than average intelligence and social responsibility and particularly if the prospective parents could tolerate

tempts at classification of *specific disease entities* have uncovered the fact that the medical profession is just beginning to explore the field of the minutiae of differential diagnosis. The difficulty of accurately classifying the so-called achondroplasias was very well emphasized in Warkany's excellent presentation of parental counseling in pediatrics.

To illustrate further, the ophthalmologist has learned to consider the term "retinitis pigmentosa" as a clinical wastepaper-basket type of diagnosis since there are now recognized seven different known hereditary modes of transmission of this interesting ophthalmoscopic picture. Neel, Dice, and Herndon in papers presented earlier have called attention to the frequency of the so-called "carrier-states." This subject was also alluded to by Warkany when he spoke of "signs and symptoms" of the traits present in other siblings and relatives of his patients. In such "carrier-states" *the individual heterozygous for a "recessive" gene* may occasionally or even constantly exhibit minimal or mild effects of the gene in contrast to the more severe or extensive manifestations of the homozygous state of the gene. Such findings merely lend emphasis to the previously made statement that the genetic counselor must meticulously study and individualize the entire family of the afflicted person before making any conclusions as to the mode of the gene transmission. It is to be admitted, however, that genetic prognosis can be made occasionally even though a definite diagnosis cannot be arrived at. This is particularly true if a careful pedigree is available.

Before leaving the subject of diagnosis, I should like to digress to speak of a fallacy and tendency exhibited by physicians in anticipating an all or none effect of a specific gene. These same physicians, however, do not expect a

lings exhibiting erythroblastosis. Breech deliveries have been known to occur more frequently in specific females and in particular families. Finally, mutation as an important cause of disease must always be kept uppermost in the mind of the counselor.

Muller has estimated that each of us carry at least eight rare hidden genes. I am aware that in telling such parents to go ahead and have children (anticipating a clinically normal individual but possibly a heterozygote genotypically) that they will further increase this pool of rare recessive genes in the general population. I cannot believe, however, that contrary advice, if followed, would materially lessen our recessive gene burden, particularly in the light of known constantly recurring mutation.

It has been my experience that many individuals after acquiring an understanding of the empiric risks through genetic counsel not infrequently decide to gamble on having their own child. Certainly no counselor has the legal right to say "thou shall not have a child."

While speaking about legal responsibility, I should like to warn all counselors to keep written copies of their opinions on file. In giving genetic information through the mail, I believe it is legally expedient to quote genetic textbooks freely and to avoid personal opinions. I am not certain to what extent the counselor can be held legally responsible for a mistaken prognosis, but this possibility should be kept constantly in mind. Osborn's further caution is to be noted, namely, that we are living in a society not eugenically oriented and in which science moves slowly. Both situations, he feels, will change; it would be wise, therefore, to be patient. Otherwise, the public's opinion may be turned against eugenics as it was some years ago.

I am optimistic about treatment of genetic disease states

the psychic, economic, and physical stress, may advise them to continue trying until they secure a normal child. This is in contradistinction to their adopting a child of even greater unknown qualities. Such advice of course presupposes a most thorough insight into the mental and physical character of the parents seldom achieved by a counselor in the course of the usual interview.

Dr. Madge Macklin has also emphasized the differences in advice that she would offer to intelligent and stable parents on the one hand and, on the other hand, the parents of low mentality, financially insecure and emotionally unstable.

To emphasize further the importance of considering the *individual as a whole,* it is mandatory that the counselor delve into a careful consideration of the influence of the maternal environment on the afflicted offspring. In this respect it is necessary that a careful history of the maternal health during the pregnancy be inquired into since it is well known that viral and other noxious environmental agents can effect changes in the fetus that closely simulate the product of a noxious gene action (phenocopy). Several of the acute viral exanthemata may not manifest themselves in the pregnant female who has sufficient immunity to protect herself but not sufficient immunity to prevent the fetus from the deleterious action of the virus. Thus, the counselor must know the probability and time of exposure of the pregnant woman in order to evaluate the possibility of noxious intrauterine viral action on the child.

Maternal hereditary states, such as diabetes, RH factor, ABO factors, anatomical defects, and others must also be carefully considered by the counselor. A diabetic mother may give birth to successive obese infants while an RH or ABO incompatibility may likewise lead to successive sib-

the gift horse more carefully than something they have paid for. I sincerely believe we obtain a rapport with the patient who pays for counseling that one does not obtain when the patient is seen without charge.

The area to which I thought I might address myself without challenge is the estimation of empiric risks. Almost without exception, the designs we have used—and I do injustice to the word "designs"—to obtain empiric risks are naïve statistically. One does not see multistage sampling used nor any of the other recent advances in sampling theory. What is worse, one cannot generally characterize the population from which a sample given in the literature was presumably drawn. Now, we all know, and I think we all appreciate, that in empiric risks we are invariably sampling from a mixed population. The population contains matings with high risk, with low risk, and possibly others. We have no notion as to what proportions of the various classes are in this mixed population, but in many cases we do have sufficient information about concomitant variables so that these, at least, could be taken into account when we attempt to obtain useful empiric risks. As Neel has said, empiric risks are a measure of our ignorance; but there are degrees of ignorance and I am sure we can refine the empiric risk figures we use by sharpening the definitions of the populations from which we are sampling, and by employing more informative sampling designs.

Before we can evaluate the importance of empiric risks or determine where greater emphasis should be placed in securing such figures, we should have some notion as to what these risks mean to the individual who is counseled. More specifically we should know when the individual who seeks guidance decides that a risk is too great. If we knew this, then we could and should place emphasis on securing

and believe that we will be able to ameliorate and prevent the ravages of many of the metabolic entities that seem to plague our elderly individuals. Early recognition and diagnosis of such metabolic entities as hypertension, arteriosclerosis, diabetes, arthritis, etc., before they reach the clinical level through careful study of all members of known afflicted families and through better provocative tests is to be anticipated. The early detection of individuals destined to be afflicted with these disease states will make it possible for medicine to ameliorate and perhaps even control the disease.

THE PROBLEM OF INADEQUATE COUNSELING

WILLIAM J. SCHULL

Oliver in his discussion of genetic counseling has already mentioned fees, and, perhaps, our experience at Michigan will be enlightening here. At Michigan we do charge for our genetic counseling. I should qualify this by saying that we charge, indirectly, for a portion of our genetic counseling. Individuals who seek guidance from us at the University of Michigan—and I am referring to personal interviews—either come to us from within the hospital on a referred basis, in which case there is no charge for our services, or they can come to the outpatient clinics to be seen on the heredity service In the latter instance they pay the entering fee that is charged every individual who seeks some sort of help through the outpatient clinic, so, in a sense, the individual is charged for our services. Personally, I do not find this especially reprehensible. It has been our experience that though the old adage goes that one should not look a gift horse in the mouth, most persons scrutinize

opinion, which makes it impossible for them to arrive at a decision.

Genetic counseling has erupted violently in the last few years, and I often wonder if we are not being stampeded into attempting to establish many counseling centers when we do not have the personnel to man adequately the ones that we have. We should certainly guard lest in our efforts to make genetic advice too readily available we dilute the quality to the point where we are not achieving the ends we hope to achieve. Man has done fairly well for a good many thousands of years in the absence of genetic counseling, and I am confident that he probably could forego our pearls of wisdom for another ten or twenty years, until we have the personnel that we need to do an adequate job.

At a counseling center should we attempt to advise everyone who seeks counsel? A categorical answer to this is clearly not possible because of the numerous "gray areas" that arise Let me illustrate one such. Not infrequently, in cases that come to us on our service, we find that the pediatrician, say, if the proband is a child, has decided that the family needs guidance, and that they need the guidance now Unfortunately, a firm diagnosis on the child has not been reached, but the diagnosis has been narrowed to two or three alternatives. We are strongly encouraged to attempt to give advice to the family. Yet obviously our advice can only be of meaning if we know precisely what the diagnosis is. If one attempts to give advice under these circumstances, he generally tries to advise for all possible contingencies, which then means recognizing as possible any one of the diagnoses. The advice then lacks immediacy and is of dubious value to the family. Moreover, the attempt to advise can be very traumatic not only to the genetic counselor but to the

the best possible figures when the risk falls within this decision-making area. At other levels the empiric risk could vary by an order or even two orders of magnitude and would be of no concern to the individual. Thus, I am sure that most persons who seek genetic advice and who are presented, say, with an empiric risk of one in a hundred, would make the same decision on the basis of this risk as they would if their chances were two in a hundred. This difference, which is small in their eyes, although it represents actually a doubling of the risk, almost certainly plays no major role in the ultimate decision that they reach. But I do believe that, by the time the risk approaches one in ten, then they begin to hesitate, and by the time the risk reaches one in two, they may decide not to have children. We should concentrate, therefore, on this area of transition where the empiric risk is taken into account in arriving at a decision. Within this critical zone we perform a disservice when we cannot provide accurate figures.

I want to comment briefly on the type of advice given. Kallmann in discussing this topic set down four rules by which to operate, rules that I think are well taken. There was one instance, however, where I, with Dr. Kallmann's permission, would like to make a small change. He said, if I recall correctly, that genetic counsel should never be given in an impersonal way. If he would permit me, I would like to change this to read: genetic advice should be given in a compassionate fashion. Impersonal means without reference to self, as I understand its use here, so that if advice is not impersonal, it must be personal. If it is personal, it must be subjective, and I doubt that two counselors would proffer the same advice. Since many of the individuals who seek advice shop for it, they are apt to be led into an area of confusion because of differences of

family and to the pediatrician, in this instance, as well. *While it would seem obvious that one would give no advice* in this situation, I know that I have been guilty and I would like to think my colleagues have also been lax in this respect. Perhaps, this is misplaced compassion.

Finally, in summarizing, let me emphasize a point that previous papers have made. Genetic counseling is certainly a very imperfect art even in the hands of the very best of us and is apt to remain so for some time to come. We should be tolerant, therefore, of other genetic counselors who are giving advice in situations that may seem somewhat less than favorable in our eyes.

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